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The American Journal of Medicine

Vol. XVII AUGUST, 1954 No. 2

Editorial

Mechanism of Pain with Peptic Ulcer . . . . . ARTHUR L. BLOOMFIELD 165

Clinical Studies

Wegener's Granulomatosis
JOHN L. FAHEY, EDWARD LEONARD, JACOB CHURG AND GABRIEL GODMAN 168

An interesting report of seven cases, with review of twenty-two additional cases from the literature of what clinically and pathologically appears to be a more or less distinct type of necrotizing granulomatous lesion referred to as Wegener's granulomatosis. Often localizing at first in the respiratory tract, it is apt to disseminate as a generalized necrotizing vasculitis, eventually particularly affecting the kidneys with uremia as the terminal event. No etiology has been established. The authors suggest that this is one of the several vascular expressions of the hypersensitivity state, to be differentiated from periarteritis nodosa, allergic angiitis, etc.

The Role of Potassium in the Prevention of Alkalosis
ROBERT E. COOKE, WILLIAM E. SEGAR, CLAUDE REED, DONNELL D. ETZWILER, MARTIN VITA, SAUL BRUSILOW AND DANIEL C. DARROW 180

The implications of this important study touch upon so many interesting aspects of electrolyte regulation, from both the physiologic and therapeutic points of view, that it should be mulled over at length. The authors explore further the interrelationships between "fixed" cations and anions under conditions designed to induce alkalosis experimentally in the normal and potassium-deficient rat. They place primary emphasis upon the role of "labile" intracellular (muscle) potassium as a readily available cation in the regulation of acid-base balance by the kidneys (rather than the reverse) and indicate the effects of potassium depletion and repletion upon such regulation particularly in respect to the development and correction of hypochloremic alkalosis. Not the least interesting rewards to the clinician are those relating to the futility of calculations of specific electrolyte requirements in fluid replacement therapy when the intracellular composition remains unknown, as it needs must be.

Dehydration with Hypernatremia, Hyperchloremia and Azotemia Complicating Nasogastric Tube Feeding . . . . FRANK L. ENGEL AND CARL JAEGER 196

In this interesting paper the authors call attention to a cause of dehydration—excessive protein intake by nasogastric tube feeding without adequate water ingestion—which may well account for

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1. Cook, M. H.; Free, A. H., and Giordano, A. S.: Am. J. M. Technol. *19*:283, 1953.
2. Gray, C. H., and Millar, H. R.: Brit. M. J. *4824*:1361 (June 20) 1953.

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otherwise inexplicable hypernatremia, hyperchloremia and azotemia in some patients. The clinical and biochemical disturbances yield readily to reduction of protein intake and increase in the provision of fluid; this may, indeed, be life-saving. The hyperosmolarity of extracellular fluid noted in patients with impaired consciousness, and attributed to neurogenic causes, may well be due to this same mechanism in some instances.

Metabolism of Copper in Wilson's Disease and in Normal Subjects. Studies with Cu-64
C. J. EARL, MILDRED JEWETT MOULTON AND BERTRAM SELVERSTONE 205

While it is quite clear that there is a disturbance in copper metabolism and in caeruloplasmin in Wilson's disease, the precise nature of this disturbance and of its significance is still obscure. The present study makes use of radioactive copper to investigate these matters further and provides additional evidence for a deficiency in caeruloplasmin synthesis, among other things. The whole problem is interestingly discussed.

N-allylnormorphine (Nalline) Action on Narcotized and Non-narcotized Subjects
A. SALOMON, P. S. MARCUS, J. A. HERSCHFUS and M. S. SEGAL 214

It is becoming increasingly apparent that the clinically useful actions of nalline are not limited to morphine intoxication alone but apply also to other narcotics, particularly in respect to respiratory depression. The present study is exploratory in this direction, an attempt to define the broader indications and contraindications of this extraordinary drug, and to expand our limited knowledge as to optimum dosage and method of administration. The evidence indicates that nalline is indeed a "safe and reliable specific antidote for narcotic-induced respiratory depression" (ineffective against barbituates) and should be available for such emergencies.

Use of Primaquine for the Treatment of Malaria in Korean Veterans
JOSEPH GENNIS, BERNARD STRAUS, MICHAEL KENNEY AND BERNARD KLEIN 223

Eradication of relapse of malaria due to presistence of exo-erythrocytic (tissue) forms of P. vivax has proved to be more difficult than suppression and treatment of the acute attack. Systematic development and testing of 8-aminoquinoline derivatives has, however, led to the discovery of several effective pamaquine analogs. Of these, according to the present study of 101 Korean veterans, primaquine is the most effective and least toxic. Occasional recrudescence, due to persistence of the erythrocytic phase, is obviated by concurrent administration of chloroquine. A therapeutic regimen combining primaquine with chloroquine is therefore suggested.

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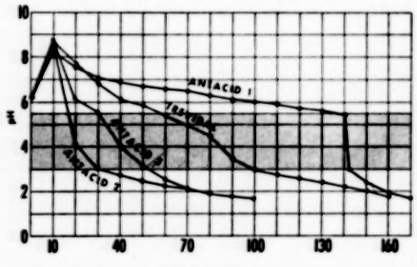

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Diphtheria. A Study of 1,433 Cases Observed during a Ten-year Period at the Los Angeles County Hospital . . . MORRIS J. NAIDITCH AND ALBERT G. BOWER 229

Diphtheria is by no means extinct even in communities with large immunization programs, moreover is showing a trend toward violent epidemic outbreaks involving a high proportion of individuals over fifteen years of age, with high mortality rates. This detailed analysis of a large experience therefore makes appropriate reading. Of special interest are the breakdown into anatomic sites of involvement, the details concerning complications of current diphtheritic infections, and the analysis of the influence of adequate and inadequate immunization on the incidence and course of the disease. The relevant literature is fully cited and annotated.

Influence of Antibiotics on Immunologic Responses in Scrub Typhus JOSEPH E. SMADEL 246

The effect of antibiotic therapy of infectious diseases upon the development of specific antibodies is a large and complex subject with many intriguing ramifications. Dr. Smadel here deals particularly with observations on rickettsial infections made chiefly in human volunteers in Malaya who exposed themselves to R. tsutsugamushi; and more generally with the over-all problem of how to make use of antibiotics and yet not interfere too much with the natural immune processes of defense. An interesting outgrowth of these studies was the development of a novel method for controlled immunization against infection.

Seminars on Antihypertensive Drugs

Treatment of Hypertension . . . . . S. W. HOOBLER 259

Dr. Hoobler begins with a classification of the clinical categories of the hypertensive state. He then considers, very briefly, the general indications and contraindications to reduction of blood pressure in hypertensives, and the place of sympathectomy, sodium restriction and drugs. The latter include Rauwolfia, hydralazine, veratrum compounds and methonium compounds and derivatives.

Conference on Therapy

Selection of Digitalis Preparations and Their Proper Administration 271

Conferences on Therapy (Cornell University Medical College)—This timely Conference dealing with the controversial subject of choice of digitalis preparations helps to clarify a situation con-

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fused by a multiplicity of such agents, each vigorously promoted. The discussion opens with a sane division into preparations of choice for the ordinary problems of management of congestive failure and those to be employed, if overdigitalization has not already occurred, for the occasional acute emergency. Digitoxin and ouabain, respectively, are considered in this connection first, then come questions of dosage, in particular the matter of fractionation of dosage in full digitalization. The allegations of greater margin of safety for certain digitalis preparations are carefully scrutinized. The limitations of animal bioassay methods are explained. These are but a few of the topics considered in what adds up to a refreshingly critical and sensible discussion of everyday problems in the use of digitalis preparations.

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Clinico-pathologic Conference (Washington University School of Medicine)—This case deals with a form of amyloidosis which is being recognized more frequently of late as presenting with refractory heart failure. The discussion of the clinical and pathologic features is interesting and informative.

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Cerebral Hodgkin's Disease. Case Report of Hodgkin's Granuloma with Cerebral Invasion . . . . . SHERWOOD B. FEIN AND VAUN A. NEWILL 291

An informative case.

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*Zelman, S.: Arch. Int. Med. *90*:141, 1952.

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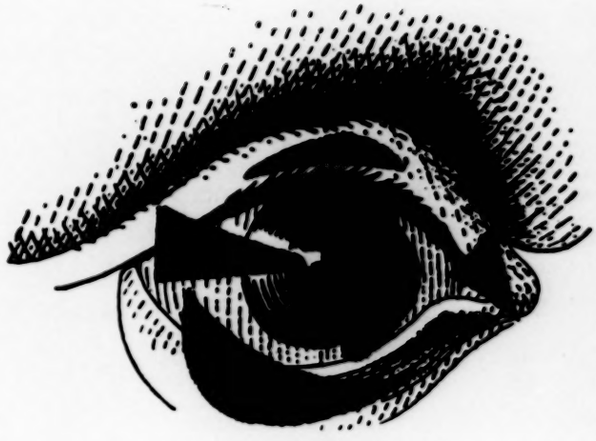

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1. Editorial: The Lancet *266*:350 (Feb. 13) 1954.
2. Stollerman, G. W. et al.: Am. J. Med. 15:645 (Nov.) 1953.
3. Wood, H. F., and McCarty, M: J. Clin. Investigation *30*:616 (June) 1951.

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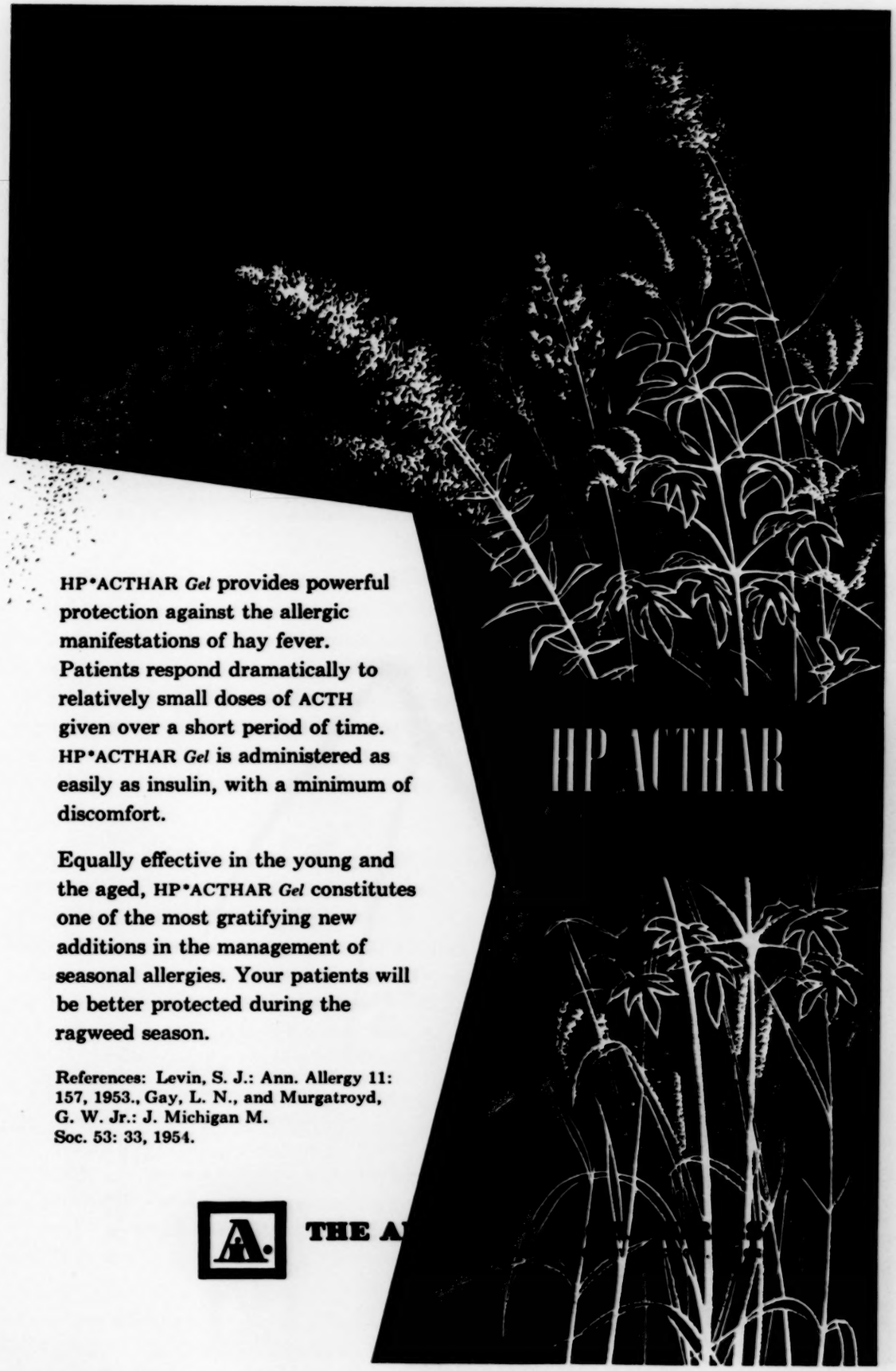

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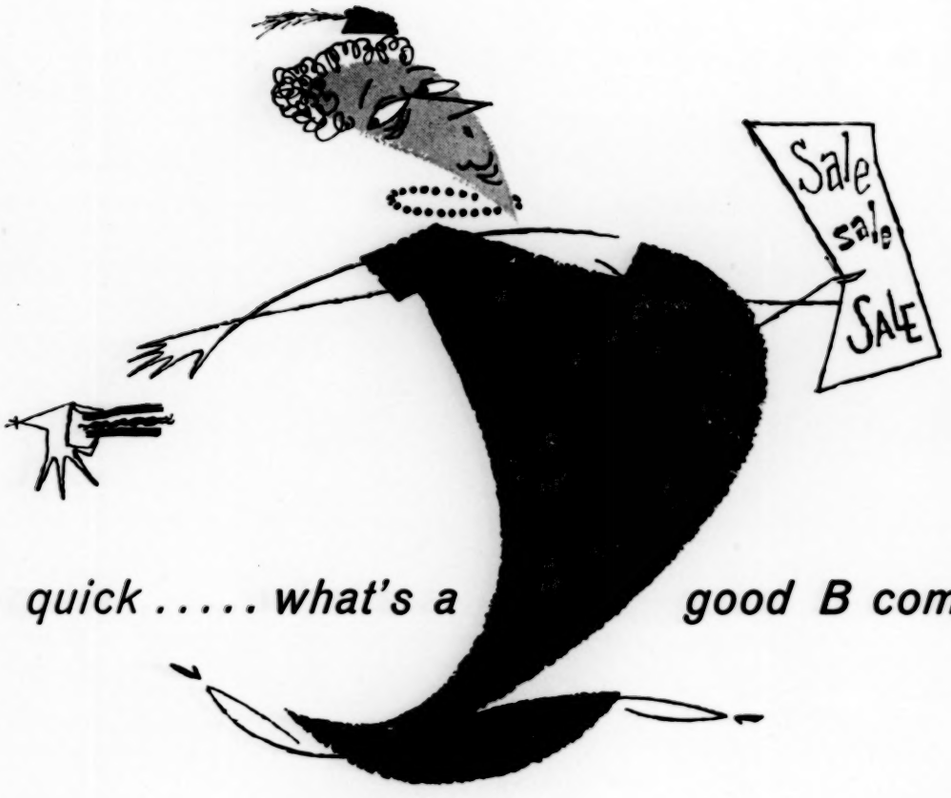

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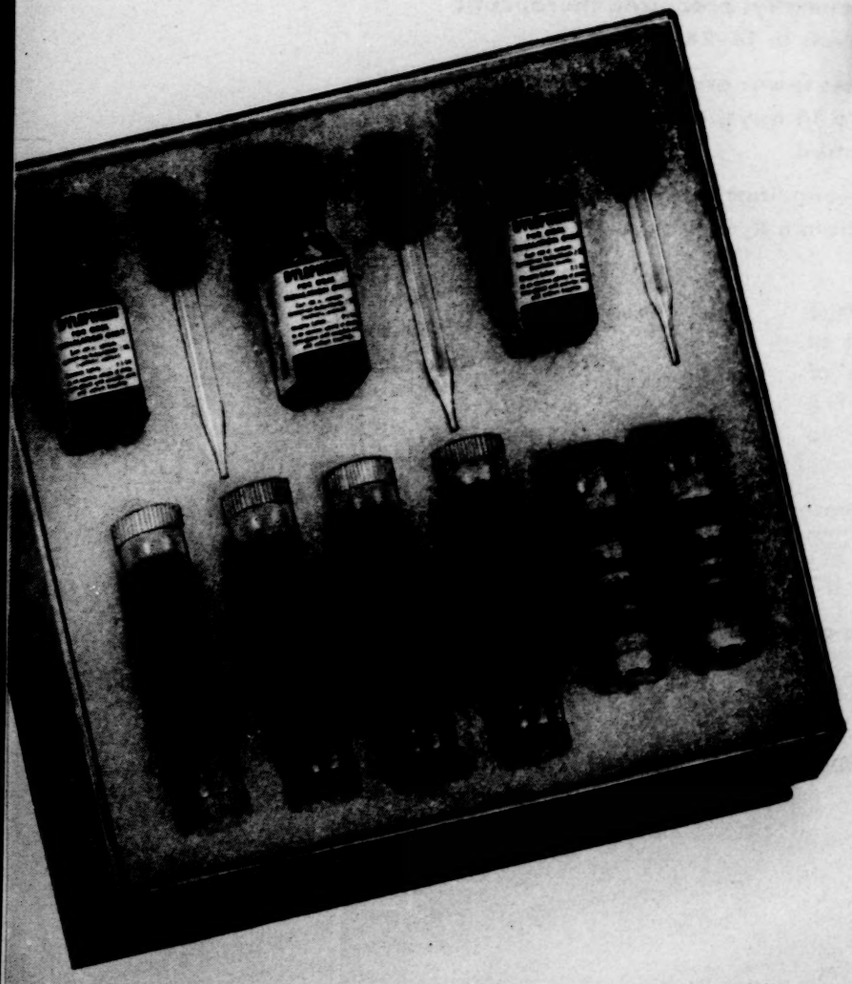

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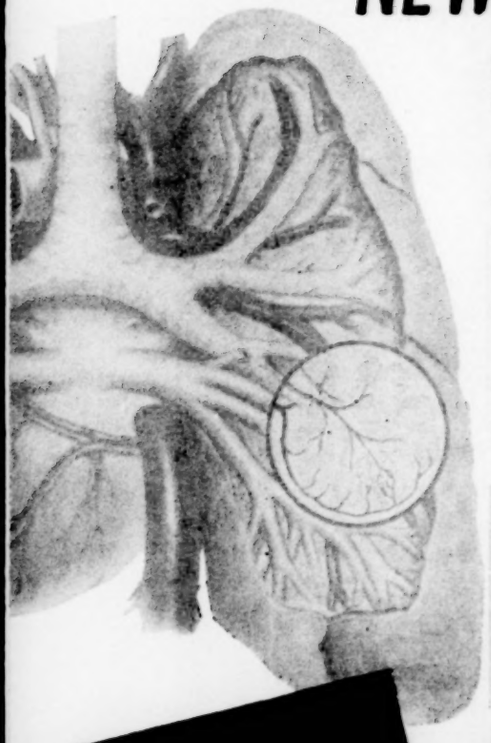

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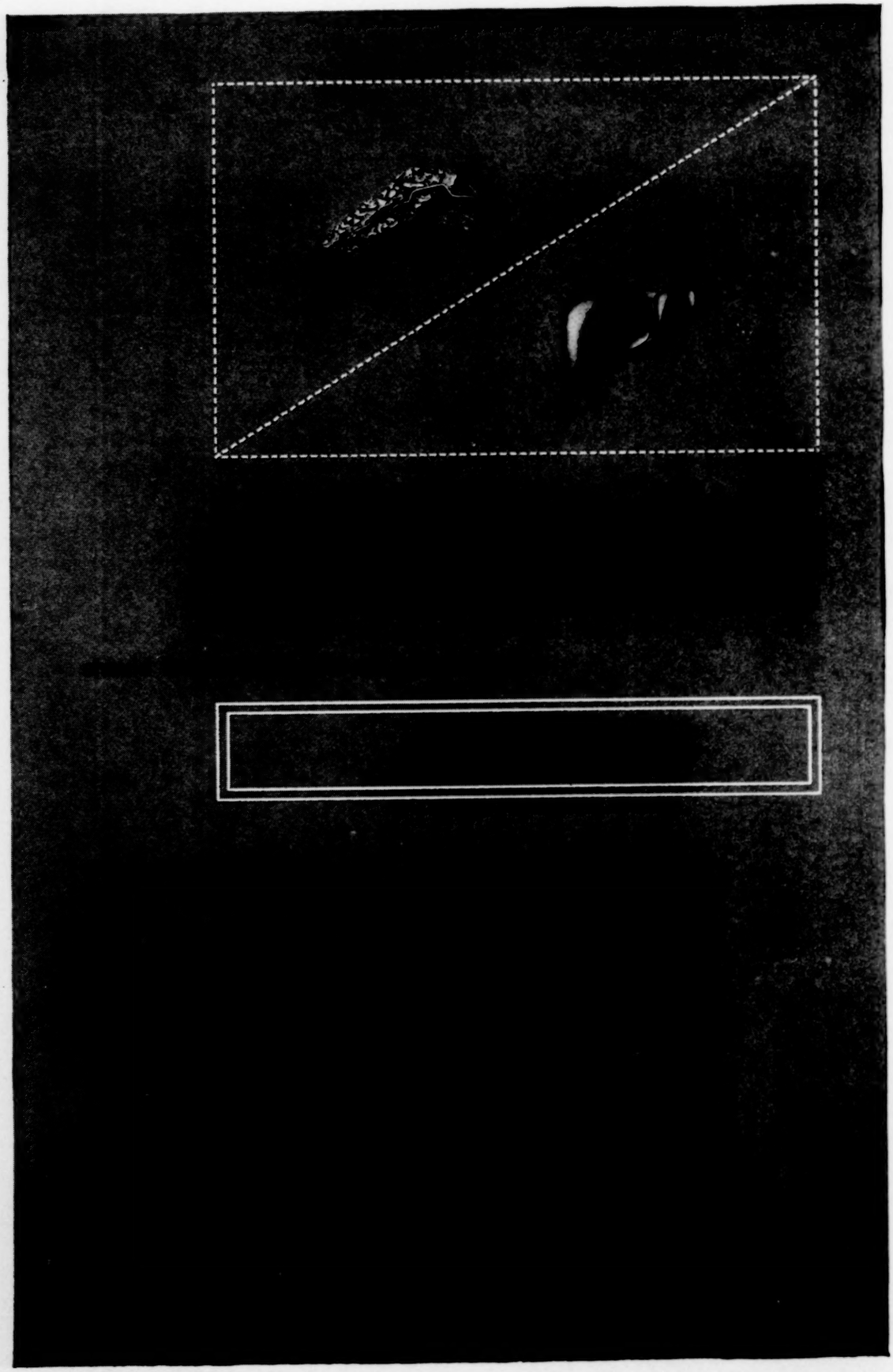

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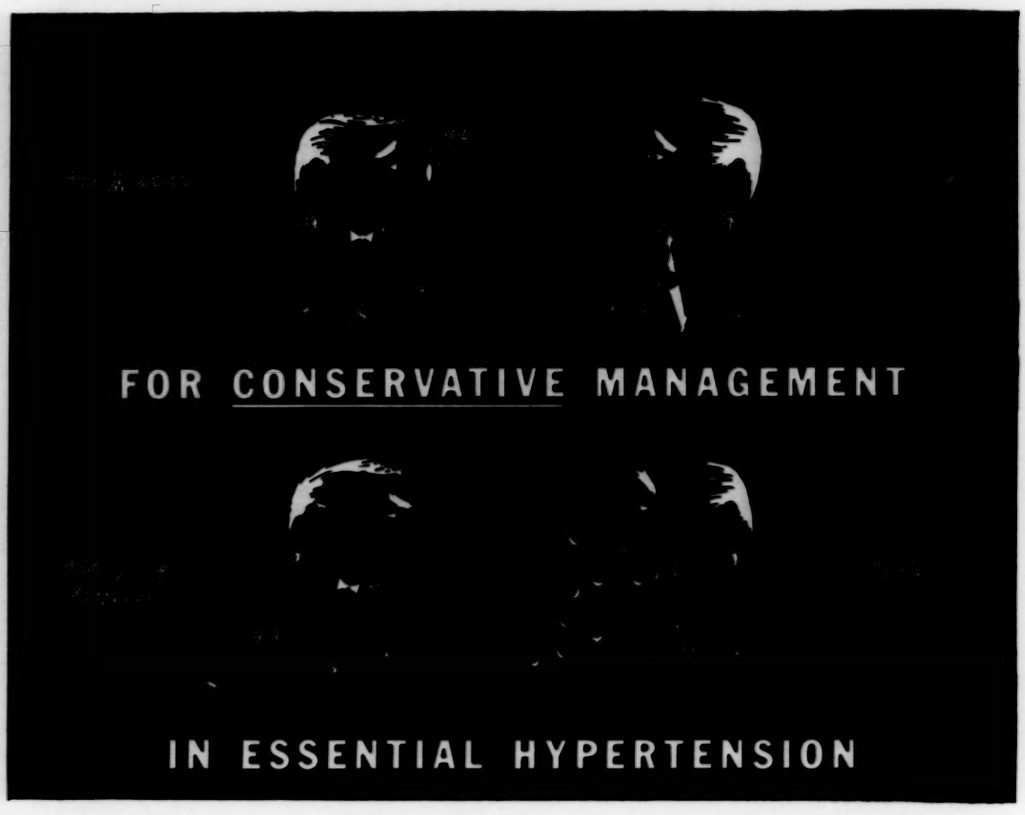

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1. Page, I. H.: In Stroud, W. D.: Diagnosis and Treatment of Cardiovascular Disease. F. A. Davis Co., Philadelphia, 1952, p. 1033.

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Schaerrer, W. C., J. Missouri M. A., 37:287.

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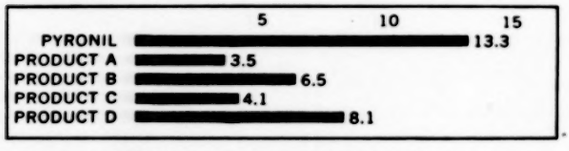

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Mechanism of Pain with Peptic Ulcer

THE exact genesis of the "indigestion"—fullness, burning, distress—so often associated with gastric or duodenal ulcer has been a disputed question for many years. As everyone knows, there are those who believe that direct irritation of the ulcer by acid gastric juice produces the "pain"[1] whereas others are of the opinion that spasm or at least some disturbance of motility perhaps in the pyloric region is the cause[2] and that the ulcer itself is insensitive. Just why there is so much partisan feeling about these two views is not clear; be this as it may, the Capulets and the Montagues never bit their thumbs at each other more energetically than the protagonists of these contradictory opinions.[3]

Now all this would not be of much importance unless some practical point were involved. This is indeed so; the presence of an ulcer clearly does not run entirely parallel with the occurence of "pain"; symptoms may disappear very quickly, long before an ulcer is healed, or an ulcer may seem to be healed although the patient still has symptoms. It is very confusing to read about relapse rates after various methods of treating peptic ulcer when the writer does not state if the relapse is a recurrence of symptoms, of lesions, or of both. An elementary concept, therefore, is that the doctor must deal with *both* symptoms and lesions; he must not only control symptoms for the sake of the patient's comfort but he must also be sure that the ulcer is healed or eliminated.

If, then, indigestion symptoms were an unfailing index of the presence of active ulcer, the whole question of treatment would be much simplified; disappearance of symptoms would mean healing of ulcer. But since this does not seem to be the case, an analysis of the pros and cons of the acid irritation versus the "spasm" theory may be of importance.

EVIDENCE AGAINST ACID IRRITATION THEORY

1. An ulcer may run its entire course to perforation without any symptoms until the accident occurs, even though the lesion is constantly bathed in acid. This has been taken by some as evidence against the explanation of pain by acid irritation. However, answer is made that the center of the ulcer may be filled with granulation tissue in which there are no nerves.

2. Against the acid irritation theory it has been pointed out that identical symptoms occur in patients who have no ulcer. It is well known that removal of gallstones may relieve patients of indigestion in no way distinguishable from that present in people with ulcer. Similar symptoms may occur with all sorts of lesions in the abdomen or, actually, as a result of cortical (nervous) disturbances. One may well argue that all these circumstances can act as triggers which fire off those motor disturbances directly responsible for the pain. To all this the answer is made that an unrecognized ulcer is present. However, this seems improbable if there are several careful negative gastrointestinal x-ray series, negative gastroscopy and correction of symptoms by such measures as psychotherapy or removal of a scarred appendix vermiformis.

3. There are records of patients whose pain persists after excision of the ulcer. This is difficult to reconcile with the acid irritation theory unless a new ulcer has formed; in the cases to which we refer no new ulcer was demonstrated.[4]

4. Indigestion identical with that seen in patients with highly acid secretion may occasionally

[1] KIRSNER, J. B. and PALMER, W. L. The problem of peptic ulcer. *Am. J. Med.*, 13: 615, 1952.

[2] HURST, A. The Sensibility of the Alimentary Canal. London, 1911. Oxford Univ. Press.

[3] BONNEY, G. L. W. and PICKERING, G. K. Observations on the mechanism of pain in ulcer of the stomach and duodenum. *Clin. Sc.*, 16: 241, 1946.

[4] BLOOMFIELD, A. L. Peptic ulcer. The relation of the lesion to symptoms and the indications for operation. *M. Clin. North America*, 8: 313, 1948.

occur in those with low acid or with anacidity. To this observation, so reconcilable with spasm as the cause of symptoms, answer may be made that there has been a mistake in measuring the acidity of the gastric juice.

5. Relief of symptoms often occurs promptly on rest, sedatives and simple diet without any change in the gastric acidity. This common observation would seem to prove that some mechanism other than acid irritation is at fault. However, the proponents of that view reply that rest has made the pain mechanism insensitive and that a film of granulation tissue has already formed over the ulcer.

6. It is a well documented observation[5] that the inflation of a small balloon inserted into the duodenum may reproduce the pain of duodenal ulcer. Such induced pain is likely to disappear immediately when the balloon is deflated. Here would seem to be incontrovertible evidence that distention of muscle, spasm or altered motility can produce indigestion symptoms. However, those in favor of the acid irritation theory ask how one can get a burning pain without acid. The syllogism seems obvious: the pain is burning in character; acid burns; therefore the pain must be produced by acid. There is, however, a large body of direct evidence that spasm or distention may produce a burning sensation. Inflation of balloons, for example, in the lower oesophagus[6] elicited such feelings as "a prickly pear," "a finger nail against a hot stove," etc. It is also asked: If spasm produces pain with peptic ulcer, why is the normal motility of the gastrointestinal tract not painful? One must, of course, assume that the spasm of ulcer indigestion is not normal motility, that there is some sort of dyskinesia, some conflict of waves, to produce these symptoms.

7. Finally, on a number of occasions in our experience gastroscopists have seen violent contractions of the pylorus at the moment when the patient declared that his pain came on, with relief as the visible spasm relaxed.

EVIDENCE FOR THE ACID IRRITATION THEORY

1. Relief of pain by alkali would seem to be strong evidence but if one probes the matter carefully several questions arise. First of all, alkali often relieves the pain in doses far too small to neutralize all the acid. Furthermore, if one observes the patient carefully relief sometimes comes not when the alkali is swallowed but when the gas which is formed is belched up, as if some alteration in tonus or in spasm had been produced. Finally, on occasion indigestion is relieved by small amounts of food which has no great neutralizing value or indeed by some non-alkaline substance.

2. While aspirating acid juice from the stomach to relieve pain could readily alter a state of abnormal tonus or spasm, it is obvious to anyone who has worked with gastric intubation that the last film of acid covering an ulcer cannot be removed. It would seem to make little difference whether the ulcer is irritated by a 1 mm. layer of tenth normal acid or whether it lies at the bottom of a big lake of juice. All this is very much like trying to measure the depth of the ocean with a foot rule.

3. Reproduction of pain by instilling acid into the stomach is not constantly effective, as everyone recognizes. It has been stated that the pain-producing mechanism must be active at the moment. At any rate, the procedure of injection could perhaps produce a disturbance of motility as well as acid irritation.

4. Activation of an ulcer by administration of steroids with increase in acidity is another point of evidence. It has been amply shown that cortisone or ACTH given over a period of several weeks may stimulate an output of excessively acid gastric juice and may lead to the formation of gastric ulcer.[7] Actually, the facts seem somewhat against the acid irritation theory of symptoms, as many "cortisone" ulcers are entirely asymptomatic until bleeding, perforation or discovery by x-ray take place.

With this brief analysis before him the reader had best form his own opinion as to the mechanism of "ulcer pain." It seems important, however, to call attention to some further recent work which has a significant bearing on the subject.

In an attempt to resolve this vexing problem it occurred to Ruffin and his associates[8] to try to control motility and acid at the same time. They added, therefore, to 200 cc. of 0.1 N HCl 2 ounces of barium sulfate and observed the pa-

[5] JONES, C. Digestive Tract Pain. New York, 1938. Macmillan.

[6] POLLAND, W. S. and BLOOMFIELD, A. L. Experimental referred pain from the gastro-intestinal tract. I. The oesophagus. *J. Clin. Investigation*, 10: 435, 1931.

[7] KIRSNER, J. B. Hormones and peptic ulcer. *Bull. New York Acad. Med.*, 29: 477, 1953.

[8] RUFFIN, J. M., BAYLISS, G. J., LEGERTON, C. W., JR. and TEXTER, E. C., JR. Mechanism of pain in peptic ulcer. *Gastroenterology*, 23: 252, 1953.

tients fluoroscopically at frequent intervals for a period of thirty minutes after ingestion of the acid-barium mixture. "The relationship between motility, 'acid-barium' at the ulcer site, and the presence or absence of ulcer pain was studied." The results were interesting. In spite of the high acid values, in only thirty-seven of one hundred tests did the subject feel pain even though the fluoroscopist could see the acid-barium in the crater. On the other hand pain was invariably associated with "abnormal motility" which ceased when "motor function returned to normal." Further observations were made with the administration of banthine® when it was found that in all but one case pain was promptly relieved but in coincidence with cessation of abnormal motility and with relaxation of the stomach. The writers conclude that "abnormal motility is the fundamental mechanism through which ulcer pain is produced."

It remains then to await rebuttal of these observations by the advocates of the acid-irritation theory.

ARTHUR L. BLOOMFIELD, M.D.

Clinical Studies

Wegener's Granulomatosis*

JOHN L. FAHEY, M.D., EDWARD LEONARD, M.D.,
Bethesda, Maryland
JACOB CHURG, M.D. *and* GABRIEL GODMAN, M.D.
New York, New York

WEGENER'S granulomatosis is a syndrome identified pathologically by necrotizing granulomatous lesions of the respiratory tract, generalized arteritis and focal glomerulitis. Clinically it may be recognized by the combination of severe sinusitis or pulmonary inflammation, variable symptoms of arteritis and terminal renal insufficiency. Since the first case report by Klinger[1] and its formulation by Wegener[2] as an entity separable from the usual forms of periarteritis nodosa, a total of at least eighteen autopsied cases have been reported, principally in journals of pathology. In this paper a brief presentation of seven more patients with Wegener's granulomatosis, one of whom (Case VII) is still living and under treatment, is followed by a description of the clinical and pathologic features of the syndrome.

CASE REPORTS

CASE I. R. K., a forty year old office worker, was admitted to Presbyterian Hospital in 1951 because of massive collapse of her left lung. Past health had been good. The collapse occurred about ten days after she had suffered a traumatic rib fracture on the right. X-ray at the time of the fracture revealed no abnormalities in the lung parenchyma. At the same time severe sinusitis developed which persisted until her death. On admission she did not appear chronically ill. Her temperature was 102°F. and blood pressure was 140/80. Nasal mucous membranes were reddened and crusted with blood. An ulcer was present on the tongue. There were physical signs of left lung collapse. Pertinent laboratory findings included a hematocrit of 34 per cent, white blood count of 12,800 per cu. mm. with no eosinophils, erythrocyte sedimentation rate of 127 mm. in one hour, and normal urine. The admission chest x-ray revealed partial collapse of the left lung and an area of increased density in the lingula of the left upper lobe. Stenosis and ulceration of the left main bronchus were seen on bronchoscopy. It appeared likely that the bronchostenosis, in the face of impaired respiratory function secondary to the rib fracture, was responsible for the massive atelectasis.

For two weeks the patient ran a febrile course. The atelectasis cleared partially but signs of disease in the lingula persisted. Cultures of bronchial secretions grew Staphylococcus aureus and a gram-negative rod. No tubercle bacilli were found. The patient's course was altered neither by a variety of chemotherapeutic agents nor by bronchoscopy, bronchodilators or mechanical exsufflation. Because of continuing morbidity, incision and drainage of the lingula was performed. On the basis of the clinical picture and the granulomatous process found on pulmonary and bronchial biopsies, a diagnosis of Wegener's granulomatosis was entertained.

The patient's postoperative course was essentially unchanged, with continued fever and cough. About three weeks passed before she improved. However, ten days before death white cells and albumin appeared in her urine, oliguria developed and blood non-protein nitrogen rose from 35 to 112 mg. per cent. ACTH, 25 mg. every six hours, was started but she died three days later, two months after admission.

Anatomic diagnoses: Necrotizing and organizing giant cell granuloma involving the lingula of the left lung and left main bronchus, with stenosis of the bronchus; arteritis and phlebitis of lung, acute and healed. Focal necrotizing

* From the Departments of Medicine and Surgical Pathology, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, and the Pathology Laboratory of The Mount Sinai Hospital, New York, N. Y.

FIG. 1. Case I. Nasal mucosa; inflamed granulation tissue containing a necrotic and infiltrated artery; hematoxylin and eosin, × 80.

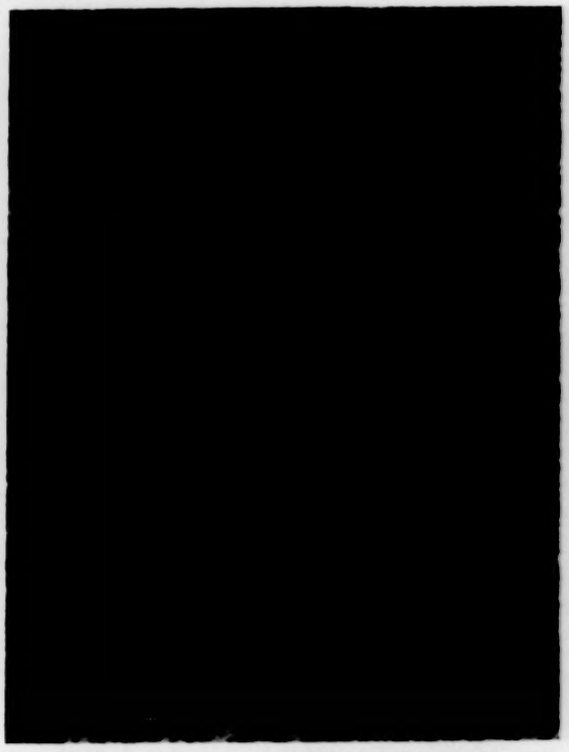


FIG. 2. Case I. Lung; typical focus of necrosis, with surrounding giant cells, granulation tissue and cellular infiltration; hematoxylin and eosin, × 400.

glomerulitis, acute and subacute; periglomerular granulomas; necrotizing renal arteritis, acute and healed; infarcts of kidneys. Acute ovarian arteritis. (Figs. 1 and 2.)

CASE II. M. C. was first admitted to the Beth-El Hosptial in July, 1951, at the age of thirty-four because of arthritis of his left knee. His health had been good until four months before, when he had two attacks of sinusitis. After treatment with penicillin hives and migratory polyarthritis developed. All of his symptoms disappeared except for pain and limitation of motion of the left knee, and this was the only positive finding on admission. Pertinent laboratory data included a normal urine, slightly elevated erythrocyte sedimentation rate, white blood count of 5,000 to 12,000 per cu. mm. with no eosinophils, and hematocrit of 41 per cent. Exploration of the knee joint revealed degenerated cartilage, a loose meniscus and inflamed synovia. The joint fluid contained no microorganisms. For the next several months the patient suffered from pain in this joint. One culture, obtained at a second operation in November, grew actinomyces. He was treated with antibiotics, including sulfadiazine, for the next ten weeks.

Signs of more generalized disease appeared in January, 1952. The patient was hospitalized in January and May because of migratory arthritis, fever to 103°F., proptosis, epistaxis, conjunctival and nasal congestion. X-rays revealed pansinusitis and normal lung fields. The urine now contained a few white cells, red cells and casts. Lupus erythematosus was suspected but no L.E. cells were found. Cortisone, given for about two weeks in dosage of 75 mg. every six hours, caused a reduction in joint symptoms but had no effect on the low-grade fever.

In June, 1952, while still on cortisone, he was readmitted because of left flank pain, bloody urine, fever and severe migratory arthritis. He appeared acutely ill. His temperature was 100.8°F. and blood pressure was 130/80. Positive physical findings were exophthalmos and signs of polyarthritis. Heavy albuminuria and hematuria were present throughout this hospitalization. The white blood count was 6,400 to 12,000 per cu. mm. without eosinophilia. Serum albumin was 3.6 gm. per cent, and globulin was 3.4 gm. per cent. The patient deteriorated rapidly. A widespread petechial rash appeared despite a normal clotting mechanism, and skin

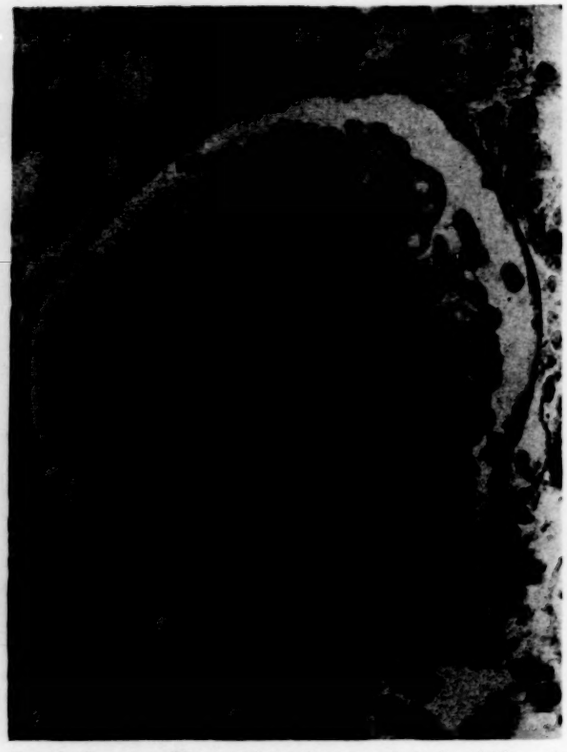


FIG. 3. Case III. Glomerulus; characteristic focal "loop" necrosis; hematoxylin and eosin, × 400.

biopsy revealed a necrotizing arteritis. The blood urea nitrogen rose on this admission from 23 to 200 mg per cent and the patient died in uremia on the ninth hospital day.

Anatomic diagnoses: Circumscribed, multiple necrotizing and organizing giant cell granulomas of the lungs; granulomatous ulcerative bronchitis; healed pulmonary arteritis. Acute necrotizing arteritis and thrombophlebitis of spleen; disseminated focal splenic infarcts. Focal necrotizing glomerulitis, acute and subacute; periglomerular and interstitial granulomas of kidneys; acute necrotizing renal arteritis. Focal necrotizing granulomas of prostate and of lymph nodes. Acute and healing arteritis of pancreas, adrenals, esophagus, intestine, testes and gallbladder.

CASE III. E. S. was first seen at Mount Sinai Hospital in January, 1951, at the age of fifty. His health had been good until about six weeks earlier when he had transient acute orchitis. About three weeks after this episode he began to complain of pleuritic chest pain, thoracic oppression and a cough productive of reddish-brown sputum. He noticed weakness of his legs, weight loss and felt sick enough to stop working. Chest x-ray revealed an infiltration of the left hilum, which had increased by the time a second film was taken two weeks later. Significant physical findings were a 2 cm. firm mass in the lower pole of the left testis and prostatic enlargement. The patient appeared chronically ill. Laboratory data included: hemoglobin, 10.5 gm. per cent; white count of 8,200 per cu. mm. with 1 per cent eosinophils; erythrocyte sedimentation rate, 54 mm. in one hour; urinalysis negative.

He was admitted three weeks after his first clinic visit. A chest x-ray now showed a 1 cm. nodule at the level of the tenth rib, suggestive of a metastatic focus. The patient's condition deteriorated rapidly. Shortly after admission he developed fever, with daily spikes of 102° to 104°F. His mental behavior became bizzare, to the point of frank delirium. Hemorrhagic necrotizing lesions spread widely over the skin of the extremities, and also caused shallow necrotic ulcerations in the mucous membranes of the mouth. A skin biopsy showed an acute arteriolitis. Four days before death there appeared signs of acute arthritis of wrist, elbow and ankle. He also developed a phlebitis of the left femoral vein. The pulmonary infiltration increased, with probable cavity formation.

The nature of his illness remained obscure. Intravenous and retrograde pyelograms were normal. Bronchoscopy was negative. No significant pathogens, bacteria or fungi were found. There was a hyperglobulinemia of 3.8 gm. per cent. The white count rose as high as 28,000 per cu. mm. without eosinophilia. Impairment of renal function was reflected in a rising blood non-protein nitrogen to 69 mg. per cent and the appearance of albumin and red cells in the urine. There was never any hypertension.

Chemotherapeutic agents did not alter the patient's course. He became comatose and died three weeks after admission.

Anatomic diagnoses: Necrotizing ulcerative granulomatous laryngitis, tracheitis and bronchitis; acute necrotizing arteritis and phlebitis of larynx and bronchi. Circumscribed necrotizing and organizing giant cell granulomas of lungs; acute necrotizing arteritis and phlebitis of lungs. Extensive, acute and healed arteritis of spleen; massive infarction of spleen. Acute focal necrotizing glomerulitis; periglomerular granulomas; acute necrotizing renal arteritis. Acute necrotizing mitral valvulitis. Necrotizing granulomas in prostate and epididymis. Granulomatous femoral arteritis and phlebitis. (Fig. 3.)

CASE IV. G. O., a thirty-nine year old office

worker, was admitted to the Mount Sinai Hospital in 1949 because of bilateral facial pain, a thick nasal discharge and weight loss of 10 pounds in two months. His past health had been good. On admission there was proptosis of the left eye and a granulomatous mass in the left antrum which had established fistulous communication with the buccal cavity. Initial laboratory data included Staphylococcus aureus in nasal cultures; hemoglobin, 14 gm. per cent; white blood count of 6,700 per cu. mm. without eosinophils; erythrocyte sedimentation rate, 70 mm. in one hour; urinalysis negative; normal blood urea nitrogen. Serum globulin was 2.3 gm. per cent, later rising to 3.5 gm. per cent. No tubercle bacilli were found in the sinus lesion. Chest x-ray was negative.

During the first nine weeks of hospitalization the sinus lesion progressed, causing bony destruction of the antrum and increasing proptosis and chemosis of the left eye. He began to have a swinging febrile course. The white blood count rose to 15,000 per cu. mm. Blood cultures were negative. A variety of chemotherapeutic agents were ineffectual. He also developed bilateral parotitis, severe orchitis and an ulnar neuritis, all transitory. By the end of the second month the sinus lesion had improved, the patient was feeling better and the fever had dropped to low-grade levels.

About three weeks before death the fairly sudden onset of acute cardiac failure heralded the final phase of his illness. It cleared promptly on an appropriate regimen although tachycardia and hypotension persisted. At the same time he was found to be uremic. Blood urea nitrogen rose steadily to 115 mg. per cent. (A few red blood cells and casts had appeared in the urine three weeks earlier, when he had been given sulfadiazine, but despite immediate cessation of the drug the abnormalities persisted.) He developed purpuric skin lesions although blood clotting studies were normal. Death in uremia occurred three months after admission.

Anatomic diagnosis: Chronic granulomatous rhinitis with necrotizing arteritis. Extensive destructive necrotizing granulomatous sinusitis. Ulcerative tracheitis and bronchitis. Multiple circumscribed necrotizing giant cell granulomas of the lungs; acute necrotizing pulmonary arteritis and thrombophlebitis; multiple infarcts of the lungs. Acute necrotizing arteritis of spleen; thrombosis of splenic, portal and mesenteric veins; extensive infarct of spleen. Acute focal necrotizing glomerulitis; acute and healing renal arteritis; multiple infarcts of the kidneys. Acute and healing arteritis of the heart, gastrointestinal tract, pancreas, adrenals and testes.

Case v. L. L., a thirty-nine year old man, was first admitted to the Mount Sinai Hospital in 1933 because of sinusitis and otitis media. He had a low-grade fever and had lost about 30 pounds in three months of illness. Examination revealed signs of a resolving otitis media, pansinusitis and ulcerative lesions in nose and larynx. By x-ray there were infiltrations of both lung bases and a lesion in the left upper lobe which was thought to contain a cavity. His urine contained 1-plus albumin, occasional red cells and casts. Hemoglobin was normal, white count was 16,000 per cu. mm. with no eosinophils. Blood urea nitrogen was 20 mg. per cent. Although cultures and guinea pig inoculations of sputum and sinus washings revealed no acid-fast bacilli, he was sent to a sanitarium with the presumptive diagnosis of tuberculosis of sinuses, subglottic region and lungs.

He was readmitted seven months later because of exacerbation of the left middle ear and mastoid inflammation. In the interval since his first admission he had continued to suffer from headache, low-grade fever and purulent sinusitis. A simple mastoidectomy was performed and he was discharged improved.

His third admission was in July, 1934, because of central nervous system symptoms which were thought to be conversion hysteria. The intranasal process had progressed to saddle nose deformity. The laryngeal lesion and the chest x-ray were unchanged. The urine still contained albumin, casts and red cells.

He was not admitted again until January, 1937, this time with hoarseness and paroxysmal difficulty in breathing which seemed to be caused by laryngeal stenosis. Biopsy showed a chronic inflammatory lesion but no evidence of tuberculosis.

The final admission was two months later. He was acutely ill with a severe exacerbation of pansinusitis and otitis media, and had a hemolytic streptococcal septicemia. Temperature ranged between 103° and 105°F. White blood count was 14,700 per cu. mm. with 14 per cent eosinophils. Urinalysis was unchanged from previous admissions. Blood urea nitrogen was not reported. Chest x-ray now revealed no abnormalities. He developed an acute arthritis of his right elbow and shoulder. Because of suspected sigmoid sinus

thrombosis, ligation of the internal jugular vein was undertaken. He died two days after the operation.

Anatomic diagnoses: Ulceronecrotic granulomatous laryngitis with acute arteritis and phlebitis. Circumscribed necrotizing giant cell granulomas of lungs; granulomatous bronchiolitis; acute focal necrotizing arteritis of the lungs. Splenic trabeculitis; acute and subacute focal necrotizing glomerulitis; focal hepatic phlebitis; acute necrotizing arteritis in the base of gastric ulcer. Chronic otitis media and mastoiditis; lateral sinus thrombosis; septicemia (streptococcus hemolyticus); purulent monarthritis.

CASE VI. G. M., a twelve year old white girl, was admitted to the Presbyterian Hospital in July, 1953, with purulent sinusitis and otitis media. Her past health had been good except for seasonal hay fever. There was a family history of hay fever and her father and brother also suffered from asthma.

About one month before admission the patient developed a purulent rhinitis and sinusitis followed a week later by fever, malaise, headache, migratory arthralgias and inflamed tympanic membranes. Laboratory data at that time revealed a hemoglobin of 12.9 gm. per cent; white blood count of 16,000 per cu. mm. with 3 per cent eosinophils. Urine contained 1-plus albumin, many granular casts and occasional leukocytes.

Rupture of the right tympanic membrane occurred, and Staphylococcus albus was cultured from the purulent drainage. Blood cultures were negative. Despite increasing penicillin dosage, addition of "triple sulfas" and myringotomy the illness progressed and the patient was referred to the Presbyterian Hospital.

On admission the temperature was 104°F., blood pressure was 110/70. External auditory canals bilaterally were swollen and filled with bloody discharge. The sinuses were cloudy to transillumination. Nasal mucous membranes were red, friable, tender and covered with exudate and grey slough. Physical examination was otherwise negative.

Laboratory findings confirmed anemia, leukocytosis without eosinophilia, and the elevated sedimentation rate noted earlier. Catheterized urinalyses revealed 2-plus albuminuria and many white and red cells. Blood urea nitrogen was 11 mg. per cent, and serum globulin 2.4 gm. per cent. A lupus erythmatosus preparation was negative. Cultures from the nose and ears contained hemolytic staphylococcus aureus but were negative for acid-fast organisms and fungi. Repeated blood cultures were negative. X-rays revealed pansinusitis without osseous destruction and, in the lung fields, multiple ill defined patchy nodular shadows. Electrocardiogram was normal.

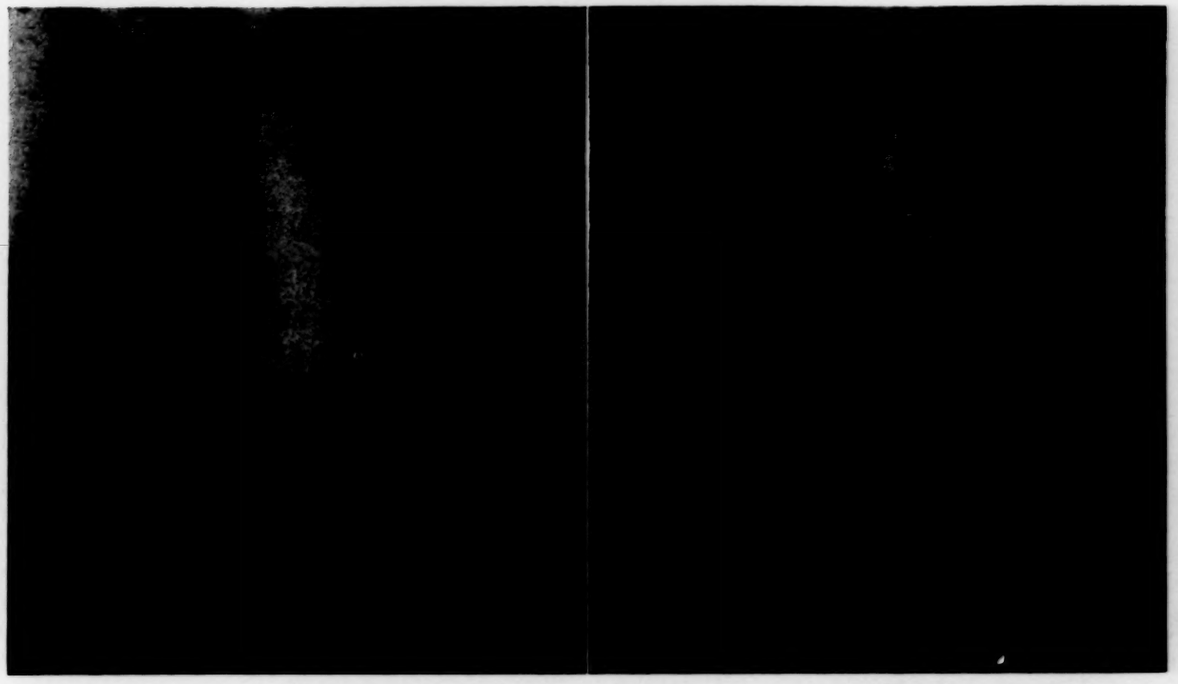
The course in the hospital was marked by high fever, progressive respiratory distress without asthma, appearance of a loud systolic basal cardiac murmur, conjunctival petechiae, a bullous lesion on the elbow and grossly bloody urine. Neither hypertension nor eosinophilia occurred. In spite of massive antibiotic therapy the patient died on the fourth hospital day. Death was associated with accumulation of blood and exudate in the bronchopulmonary passages.

Anatomic diagnoses: Granulomatous sinusitis with necrotizing arteritis. Multiple necrotizing granulomas of lungs; acute necrotizing pulmonary arteritis; focal granulomas and acute necrotizing arteritis of spleen. Acute focal necrotizing glomerulitis; acute renal arteritis; Endocarditis and myocarditis; focal coronary arteritis. Acute arteritis in adrenals and lymph nodes.

CASE VII. J. M. was first admitted to the Presbyterian Hospital in April, 1951, at the age of thirty-eight because of fever and pleuritic chest pain. Previous health had been excellent, without allergy or exposure to chemotherapeutic drugs. For two years he had been a metal grinder but exposure to silica was minimal.

About a month before admission his illness began insidiously with sinusitis, low-grade fever and cough. Because of increasing fever, pleuritic chest pain and bloody sputum he entered the hospital. He did not appear acutely ill. Temperature was 103.2°F., blood pressure was 130/70. Positive physical findings were limited to signs of consolidation at the left lung base, confirmed by x-ray. (Fig. 4A.) The hematocrit was 36 per cent. White blood count was 16,000 per cu. mm. with 1 per cent eosinophils. Erythrocyte sedimentation rate was 96 mm. in one hour. One urinalysis was normal, another showed 1-plus albumin and occasional casts. Initial sputum cultures grew Streptococcus viridans. Repeated searches for tubercle bacilli were negative. Cold agglutinins, brucella and tularemia agglutinins were negative. Sinus x-rays were clear.

A picture consistent with unresolving pneumonia, which failed to respond to massive doses



4A 4B

FIG. 4. Case VII. A, chest x-ray prior to lobectomy showing infiltration in left lower lobe; B, twenty months later. Note cavity and scattered densities in remaining left lung field (left upper lobe); right lung is clear.

of antibiotics, eventually led to left lower lobe pulmonary resection. Recovery was uneventful.

He did well for two months but then from September through December he suffered from a severe, destructive pansinusitis which progressed despite multiple antral washings and bilateral Caldwell-Luc procedures. By this time his urine was definitely abnormal, with 2-plus albumin, white cells and casts. On the basis of a biopsy of the sinus tissue, and its similarity to the material removed at lobectomy, the diagnosis of Wegener's granulomatosis was made in December, 1951.

Up to the time of writing (October, 1953) the disease has persisted in several areas. Continued sinusitis caused, in a few weeks, partial destruction of the walls of the sphenoid and ethmoid sinuses, and collapse of the septum with a saddle nose deformity. Proptosis, episodes of chemosis, and papillitis and blindness in the left eye suggest orbital invasion by granuloma. By x-ray there are signs of a widespread condensing osteitis of the sinus walls. Although the sinusitis has abated in recent months, persistent frontal head pain has required narcotics to the point of addiction.

Pulmonary infiltrates were detected in the remaining left lung in December, 1951. They slowly enlarged, with eventual cavity formation. (Fig. 4B.) The right lung has been free of disease. Sputum flora has varied but while the patient received prophylactic antibiotics the predominating organism has been Staphylococcus aureus. Candida albicans and Actinomyces bovis have been grown infrequently, not consistently enough to be implicated as pathogens. Several attacks of acute pneumonitis have occurred; but chemotherapy and recent thoracotomy drainage of necrotic areas have helped to control secondary infection. The patient has never received sulfa drugs.

Throughout his course signs of renal damage have persisted: 1–3 plus albuminuria, with occasional red cells, white cells and casts. At times albuminuria has been minimal. Blood urea nitrogen and urine concentration are normal. Transient azotemia during dehydration and a moderately reduced phenolsulfonphthalein excretion are the only signs of functional impairment. There is no hypertension.

He has had two attacks of laryngitis and granulomas were seen on the vocal cords. An episode of non-specific prostatitis was also attributed to granuloma. There has been no enlargement of liver, spleen or lymph nodes. No cardiac abnormalities were found except for

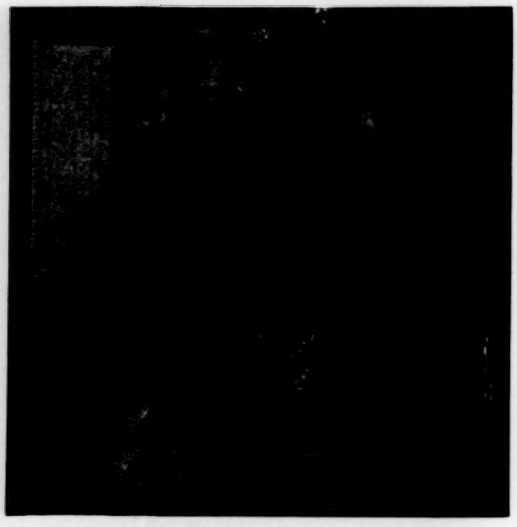


FIG. 5. Case VII. Resected left lower lobe of lung; partly necrotic granulomatous mass occupying the posterior basal segment.

transitory tachycardia and minor electrocardiographic T-wave changes. Skin, gastrointestinal tract, skeletal, muscular and nervous systems remain unremarkable.

Temperature usually varies from 99° to 101°F. There is a moderate anemia. The white blood count ranges from 11,000 to 16,000 per cu. mm. with 1 to 3 per cent eosinophils (one count of 8 per cent). The erythrocyte sedimentation rate has gradually fallen to 25 mm. in one hour. There is no hyperglobulinemia.

The patient has been taking cortisone (100 to 200 mg./day) or ACTH for nineteen months. There is fairly good evidence that these drugs controlled the intensity of the inflammatory process as well as fever and pain. Withdrawal was followed by marked chemosis, tracheitis, increased pain and fever. Large doses of ACTH (200 mg./day) were used successfully after cortisone became ineffective. Administration of nitrogen mustards intravenously was followed by a transient increase in chemosis, rise in blood urea nitrogen and then a ten-day remission in the intensity of sinus pain. Further study is needed to evaluate the effect of this drug. Radiotherapy, triethylene melamine, stilbestrol, testosterone and snake venom produced no change.

The resected specimen of the lung (May, 1951), consisting of left lower lobe and seven lymph nodes, contained a large smooth firm mass 9 by 8 by 3 cm. On section the mass was found to be rubbery in consistency and mottled yellow-green in appearance. The bronchus leading to the involved segment was grossly thickened and the lumen narrowed. (Fig. 5.)

Microscopically, the mass was found to consist of confluent areas of necrosis with giant cells, histiocytes and large sheets of granulation tissue. The walls of many bronchi were destroyed by the granulomatous process, which also involved the walls of some blood vessels. Many fibrotic medium-sized arteries and veins were also present.

A biopsy of the maxillary antrum (October, 1951) revealed granulation tissue densely infiltrated with polymorphonuclear leukocytes, plasma cells and lymphocytes.*

SUMMARY OF PATHOLOGIC FINDINGS

In four of the seven cases the upper respiratory passages (nose, paranasal sinuses, nasopharynx, glottis or epiglottis) were involved in a destructive necrotizing granulomatous process. Histologically, such affected areas were composed of granulation tissue with variable numbers of giant cells, and foci of necrosis in the depths of which acutely necrotic and inflamed small vessels were occasionally found.

In all cases, necrotizing giant cell granulomas were present in the lungs and bronchi. These were usually circumscribed nodules which, on microscopic examination, contained confluent areas of necrosis, infiltrations of mononuclear and giant cells, and wide areas of granulation tissue with many new necrotic foci. Active or healed pulmonary vasculitis was present in every case, most often in the region of the necrotizing lesion.

In the kidneys of all autopsied cases focal necrotizing, thrombotic glomerulitis, more or less widespread, was the rule. In the subacute phase these lesions showed a tendency to heal by capsular epithelial proliferation (crescent formation) and by granuloma formation. In addition, focal granulomas were encountered in the renal interstitium often periglomerular in location.

Splenic lesions, ranging from small foci of necrosis to total infarction, were observed postmortem in all cases, apparently dependent upon unusual widespread trabecular and follicular arteritis. Scattered granulomas in the spleen were also encountered in some cases.

* In May, 1954, the patient's clinical status was essentially unchanged. He became blind when ACTH was discontinued, but regained some vision when the drug was resumed.

Active and healed necrotizing inflammatory lesions of small arteries and veins, and their sequelae in the form of infarcts, hemorrhages, thromboses and aneurysms were found in the lungs in all cases and in the kidneys in five of the six autopsied cases. Vascular lesions in other organs (heart, gastrointestinal tract, adrenals, testes, pancreas) occurred less frequently.

Scattered focal granulomatous lesions, often frankly necrotic in character and usually containing giant cells, were found in various extrarespiratory locations such as spleen and kidneys, and less frequently in the prostate, epididymis, lymph nodes and walls of large blood vessels.

Acid-fast organisms, fungi or other specific organisms could not be demonstrated in the tissues of any case.

These anatomic findings will be presented in greater detail in a subsequent report.*

CLINICAL FORMULATION

The syndrome described by Wegener forms the basis for the selection of cases described in this report. Table 1 presents a summary of the cases in the medical literature that fulfill the clinical and pathologic requisites.[1–14] Several cases[15–21] have been omitted because of atypical features or insufficient published data to allow evaluation. Despite great variability in the histories of these patients, enough common characteristics emerge to form a rather striking clinical picture. The diagnosis may be suggested by persistent respiratory tract inflammatory lesions of unknown cause, especially if accompanied by signs of renal damage; or by a clinical picture of arteritis with granulomas in one or several sites.

The disease affects men and women of all ages, most frequently in the fourth and fifth decades. It seems to appear in persons of good previous health; generally without histories of allergy, asthma or exposure to sulfa drugs. The duration is brief, six months on the average, and the outcome in recognized cases would appear to be fatal. At times the illness runs an intermittent or subacute course for two or more years.

The first symptoms are often referred to some part of the respiratory tract. There may be a persistent sinusitis or rhinitis which in many instances is severe enough to cause ulceration and bony or cartilaginous destruction. Or attention may first be directed to the lungs because of chronic cough, hemoptysis or unresolving pneumonia. A chest x-ray frequently reveals non-specific parenchymal infiltrations, or nodular densities which suggest neoplasm or tuberculosis. Any part of the lung may be involved. In many cases constitutional symptoms are out of proportion to the intensity of the local process and the patient may first seek help because of weakness, fever or progressive weight loss. In fact, sometimes the main clinical features are consistent with a panarteritis, and the respiratory tract disease is incidental or not detected.

Whatever the local lesion, it generally does not respond to the usual therapeutic measures: sinusitis persists despite drainage and chemotherapy; pulmonary lesions progress to the point where surgical intervention is necessary. With extensive cartilaginous and bony destruction in the upper respiratory tract, saddle nose deformity may appear; orbital involvement may result in papillitis, chemosis and exophthalmos; or extension downward may establish fistulous communications with the buccal cavity. The inflammatory lesion is not limited to these areas and patients may suffer symptoms referable to other organs. Episodes, often transient, of arthritis, neuritis, carditis, parotitis and prostatitis have been seen. Extensive studies fail to implicate any micro-organism as a causative agent, and antibiotics seem to do nothing except help control secondary infection. In certain instances the process seems to subside without relationship to any therapeutic measures.

In the midst of this picture, sometimes when the disease appears to be subsiding, signs of renal damage appear, often heralded by moderate albuminuria and variable numbers of red cells, white cells and casts in the urine. There may be frank hematuria and oliguria, and in some patients the interval between the first appearance of renal disease and death in uremia may be as brief as ten days. Often renal insufficiency alone dominates the terminal phase of the syndrome but frequently this is associated with an acute picture consistent with a generalized arteritis. High fever, arthritis, widespread hemorrhagic lesions of skin and mucous membranes, and signs of pulmonary or myocardial damage may be noted in the last days or weeks of illness.

The course is almost always febrile. Hypertension is uncommon though it may have occurred terminally in one or two patients. Lymphadenopathy and hepatomegaly have been absent. Anemia, leukocytosis and elevated

* Godman, G. and Churg, J. *Arch. Path.*, in press.

TABLE 1

CLINICAL FINDINGS IN TWENTY-NINE CASES OF WEGENER'S GRANULOMATOSIS

Case No. and Reference	Age and Sex	Duration (mo.)	Initial Complaint	Respiratory Tract		Renal		Other Organ Manifestations				Remarks
				Upper Respiratory Lesions	Chest X-ray	Terminal NPN or BUN	Albumin or Abnormal Sediment	Skin	Joints	Neurologic	Other	
1 (1)	70, M	12	Severe sinusitis	*	No report	196	+	..	+	..	Proptosis	Sinusitis prominent; nephritis unsuspected; cause of death ? renal failure
2 (2)	38, M	6	Maxillary pain, saddle nose	†	Infiltrate, RLL	...	+	+	+	..	Stomatitis	Widespread respiratory tract lesions; terminal uremia
3 (2)	36, F	18	Severe rhinitis	†	Pneumonitis, LLL	...	+	..	..	..	Heart (EKG changes)	Destructive rhinitis with renal damage; terminal pneumonitis
4 (2)	33, F	?	Severe sinusitis, headache, fever	†	No report	...	+	+	..	..	Mouth ulcer	Ulcerative respiratory tract lesions; terminal uremia
5 (3)	44, M	4	Rhinitis, epistaxis	†	Shadow, left hilus	140	+	..	..	..	.....	Rhinitis; hilar lesion thought to be tumor; terminal uremia
6 (3)	42, F	1	Ear pain and discharge	*	Infiltrates, both lungs	...	+	..	..	...	.....	Brief, unremitting course with death in uremia; tuberculosis and nephritis suspected
7 (4)	21, F	30	Catarrh, dyspnea, dysphagia	*	Infiltrates, bilateral	...	+	..	+	+	.....	Recurrent symptoms referred to joints, heart, respiratory tract and kidneys
8 (5)	35, F	8	Weakness, cough, night sweats	..	Shadow, LLL	...	+	..	..	+	Heart failure	Course suggested polyarteritis; death in cardiac failure; mediastinal mass not mentioned
9 (6)	67, F	13	Saddle nose, fever, wasting	†	Interstitial fibrosis	102	+	..	..	..	Parotitis	Destructive rhinitis; weight loss, fever, rising globulin; sarcoid suspected; terminal uremia
10 (7)	38, M	?	Nasal bleeding	†	No report	...	..	+	..	..	Ulcers on tongue	Bronchiectasis; mediastinal tumor suspected; scanty data
11 (7)	50, F		Myalgia, rash, hemoptysis	..	Congestion	71	+	+	..	+	Pulmonary congestion	Lung lesions, with hemoptysis; then generalized arteritis, renal insufficiency
12 (8)	34, F	8	Gum ulcer, cough, fever, wasting	*	Apical lesion with fluid	...	+	..	..	..	.....	Persistent gum ulcer, lung lesion, fever, weakness; Diagnosis: ? lung abscess, pansinusitis, sepsis
13 (8)	62, F	3	Purulent sputum, fever	..	Bronchiectasis, basal	257	+	..	..	..	.....	Symptoms suggested pulmonary infection but little antibiotic response, then sudden renal failure
14 (9)	57, F	3	Hearing loss, pain in ear	*	Infiltrates, both lungs	...	+	..	..	..	.....	Pulmonary and renal findings suggested renal tumor with metastases
15 (10)	23, M	5	Rhinitis, sinusitis	†	No report	320	+	..	..	..	.....	Brief course of severe sinusitis and rhinitis; death in uremia
16 (11)	69, F	5	Cough, fever, cachexia	..	Infiltrates, both lungs	220	+	..	..	+	.....	Short course with pulmonary and systemic symptoms, then sudden renal failure; polyarteritis suspected
17 (12)	70, M	2	Fever, chest pain	..	Infiltrates, both lungs	174	+	..	..	..	.....	Fever and bloody pleural effusion; brief course with death in uremia
18 (12)	41, F	14	Sinusitis	*	Infiltrates, both lungs	300	+	+	+	..	Corneal ulcer	Persistent respiratory tract lesions; arthritis, skin rash; death in uremia
19 (13)	49, M	3	Nasal ulceration, sinusitis	†	Infiltrate, apical	84	+	..	..	+	Heart failure	Progressive nasal and sinus lesions; heart failure and uremia terminally
20 (13)	51, M	6	Rhinitis, larnygitis	†	Congestion	270	..	..	..	+	Heart failure	Similar to above case. Diagnosis in both: polyarteritis nodosa and nasal granuloma
21 (14)	27, M	7	Hemoptysis, weight loss	..	Infiltrates, LLL and RLL	131	+	+	+	..	Stomatitis	Lung lesion, resected; then recurrence, followed by arteritis and uremia
22 (14)	54, M	2	Dyspnea, cough, fever	..	Infiltrates, both lungs	154	+	..	+	..	.....	Widespread lung lesions; progressive azotemia; ? pulmonary or renal death
R. K.	40, F	2	Sinusitis, atelectasis	*	Infiltrate, LUL	112	+	..	..	..	.....	Severe sinusitis and lung granuloma, followed by sudden renal failure
M. C.	34, M	14	Sinusitis, arthritis	*	Neg. 1 month before death	200	+	+	+	..	.....	Main problem migratory arthritis and fever; terminal acute arthritis, petechial rash, uremia
E. S.	50, M	3	Orchitis, weakness, weight loss	..	Infiltrate, left	69	+	+	+	+	Prostatitis, orchitis	Testis and lung lesions suggested malignancy; terminal arthritis, skin lesions, uremia
G. O.	39, M	5	Severe sinusitis	†	Effusion, infiltrate	115	+	+	..	+	Parotid, heart, testis	Destructive sinusitis; transient lesions in other organs; sudden onset of petechial rash, uremia
L. L.	39, M	48	Sinusitis, otitis	†	Infiltrates, one cavity	...	+	+	..	..	.....	Long history of sinusitis and signs of renal damage, ? septicemia terminally
G. M.	12, F	1	Sinusitis, otitis	†	Infiltrates, both lungs	11	+	+	+	..	Heart murmur	Severe sinusitis and otitis media; marked pulmonary and renal disease; rapid course
J. M.	38, M	32+	Pneumonia, sinusitis	†	Infiltrates, LLL and LUL	...	+	..	..	..	Prostatitis, papillitis	Destructive sinusitis; granuloma, causing progressive lung destruction; renal damage; subacute course

* Inflammatory upper respiratory tract lesion.
† Inflammatory and destructive upper respiratory tract lesion.
+ = abnormality present.

erythrocyte sedimentation rate are usually found. Eosinophilia (over 9 per cent of total white blood count) occurred in only two of nineteen cases in which counts were reported. Serologic tests for syphilis are negative. Hyperglobulinemia was observed in several of the patients tested.

ACTH and cortisone seem to have controlled systemic symptoms and inflammatory lesions in one patient (J. M.) but this case is somewhat atypical because of a prolonged subacute course. No other drugs are known to be effective though nitrogen mustards deserve further study.

DIFFERENTIAL DIAGNOSIS

Anatomically, Wegener's granulomatosis is characterized by three morbid features: (1) necrotizing granulomatous lesions in the upper air passages, lower respiratory tract or both; (2) generalized focal necrotizing vasculitis involving both arteries and veins, almost always present in the lungs and more or less widely disseminated in other sites; (3) glomerulitis, characterized by necrosis and thrombosis of loops or lobes of the capillary tuft, capsular adhesions and evolution as a granulomatous lesion. No one or two of these pathologic changes, in the absence of the others, defines the syndrome anatomically.

To be differentiated from the syndrome thus defined are a number of conditions which run in a spectrum from pure necrotizing and granulomatous processes without vasculitis through mixed forms to pure arteritis without granulomas. (1) The clinical and pathologic features of Wegener's granulomatosis may at times suggest the diagnosis of a specific infectious granulomatous disease. However, the agents of tuberculosis, lues, tularemia, blastomycosis, histoplasmosis, glanders and lymphopathia venereum have never been identified in any case. Isolated cultures of actinomyces found in two cases are not considered etiologically significant. Nor are generalized necrotizing vascular lesions likely to be found in these infectious granulomas. (2) The lesions of Boeck's sarcoid sometimes involve vessel walls[22] and may be concentrated in those sites affected in Wegener's granulomatosis. But the granuloma of sarcoid is essentially nonnecrotizing and cases of sarcoidosis have not been known to develop necrotizing glomerulitis. (3) The progressive destruction of the upper air passages which often occurs in Wegener's granulomatosis may suggest the diagnosis of agnogenic progressive lethal granulomatous ulceration of the nose and face ("granuloma gangrenescens").[23–26] However, the manifestations of this uncommon condition usually remain localized in the midline facial tissues. Disseminated visceral granulomas apparently do not occur. And with a few exceptions,[25,26] the cases which have been carefully studied have had neither vascular nor renal lesions. (4) Because of the vascular disease, Wegener's granulomatosis has often been considered to be a respiratory-renal subtype of periarteritis nodosa.[2,12,14] The "classical" periarteritis nodosa known to the older literature involves principally medium-sized arteries, and the only extravascular lesions are infarcts secondary to the interrupted blood supply. However, in many cases designated as periarteritis nodosa there are other extravascular lesions, such as parenchymatous changes in the spleen (trabeculitis, granulomas), or focal glomerular nephritis. Some authors differentiate these cases from the classical periarteritis nodosa and place them in special categories: hypersensitivity angiitis[27] or the microscopic form of periarteritis nodosa.[28,29] In this group the vascular lesions involve chiefly small vessels, both arteries and veins; they are usually acute and fairly numerous.[27] In our cases small vessels are likewise involved but with acute and healing lesions in all stages; and with considerable variation in the extent of the vasculitis, the lesions being infrequent in many patients. Pulmonary vasculitis is uncommon in classical periarteritis nodosa, occurs more frequently in hypersensitivity angiitis, and was found in every one of our own cases. Wegener's granulomatosis further differs from the arteritides already discussed by virtue of the extensive necrotizing granulomatous lesions concentrated in the respiratory tract, a manifestation which evidently precedes in most cases the appearance of disseminated vascular disease. (5) Granulomatous or vascular lesions are found in certain patients who present clinical evidence of allergy (asthma, eosinophilia). The pathologic findings include extravascular granulomas and necrosis, necrotizing angiitis affecting small vessels, and often splenic or focal glomerular lesions.[29,30] In one group, of which Loeffler's syndrome may be a member, granulomas (or eosinophilic infiltrations) predominate; and the vascular lesions, demonstrated in the lungs of a few autopsied cases, are not generalized.[31–35] In another group composed of asthmatics who develop signs of arteritis terminally, vasculitis is

predominant. This syndrome has been described by Churg and Strauss as allergic angiitis and granulomatosis.[30] Although the similarity of the tissue reactions suggests a relationship to these cases, Wegener's granulomatosis may be distinguished on the basis of (*a*) the marked predominance of necrotizing granulomatous lesions in the respiratory tract and their aggressive nature; (*b*) the regular occurrence and severity of the renal lesions; and (*c*) the usual absence of clinical stigmata of allergy, or tissue eosinophilia. One of our cases, G. M., presented all the features of Wegener's granulomatosis but also had a allergic history and tissue eosinophilia characteristic of the disease patterns referred to in this paragraph.

PATHOGENESIS

Granulomas,[36] vasculitis[37,38] and glomerulonephritis[37,39] may each be found in hypersensitivity states, either in those produced experimentally or in human disease. The occurrence in the same syndrome of all three lesions suggests that Wegener's granulomatosis is a disease of hypersensitivity. The clinical data indicate that the respiratory tract lesions usually precede the vascular and renal disease. But the causes of the peculiar concentration of lesions in the respiratory tract and their relation to the angiitis and nephritis that follow are not completely understood. The tissue reactions are basically similar to those found in a number of conditions discussed. But the characteristic combination of these tissue changes and the generally recognizable clinical picture accompanying them would appear to justify the definition of Wegener's granulomatosis as a syndrome separable from related categories of vascular and granulomatous disease.

SUMMARY

Seven new cases of Wegener's granulomatosis are reported. One patient has been observed for almost two years following establishment of the diagnosis. In addition, twenty-two cases from the literature are reviewed.

The clinical syndrome typically begins with a severe, often destructive sinusitis or rhinitis, or with a persistent pneumonitis. Signs of renal damage and generalized vasculitis accompany or follow the respiratory disease. The illness ends fatally in the cases so far recognized, with arteritis or uremia dominating the terminal picture.

Pathologic findings include necrotizing granulomatous lesions in the respiratory tract, generalized focal necrotizing vasculitis and glomerulitis.

As a syndrome, Wegener's granulomatosis can be distinguished from other related categories of arteritis and granulomatous disease. No specific etiologic agent has been identified. A mechanism of hypersensitivity apparently operates in the pathogenesis of the illness.

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The Role of Potassium in the Prevention of Alkalosis*

ROBERT E. COOKE, M.D.,† WILLIAM E. SEGAR, M.D., CLAUDE REED, M.D., DONNELL D. ETZWILER, M.D., MARTIN VITA, A.B., SAUL BRUSILOW, A.B. *and* DANIEL C. DARROW, M.D.

New Haven, Connecticut

A RELATIONSHIP between serum bicarbonate concentration and the sodium and potassium content of skeletal muscle was described in experimental animals in 1946.[1] In metabolic alkalosis and acidosis muscle potassium varies inversely with the concentration of bicarbonate in serum, while intracellular sodium varies directly.[2] However, in compensated respiratory acidosis in which serum bicarbonate concentration is elevated but serum pH is low there is a slight increase in muscle potassium and slight decrease in intracellular sodium.[3] The fundamental relationship between the composition of extracellular fluid and muscle composition must therefore be expressed in terms of serum pH rather than bicarbonate concentration. The possible significance of these relationships between extracellular and intracellular fluids of muscle has been discussed by Cooke and Segar.[4]

The role of changes in muscle composition during recovery from metabolic alkalosis when potassium chloride is administered has been described by Cooke et al.[5] During recovery the retention of potassium within cells is greater than the release of intracellular sodium. This finding indicates that reduction of serum bicarbonate is the result of exchange of retained potassium for intracellular hydrogen ions. This conclusion has been confirmed by Orloff et al.[6] in nephrectomized rats treated with a mixture of potassium chloride and potassium bicarbonate.

Nevertheless, exchange of ions between muscle cells and extracellular fluid does not account for the persistence of hypochloremic alkalosis in potassium deficiency unless alterations in renal function are also present.

In preliminary experiments an attempt was made to produce metabolic alkalosis without potassium deficiency. It was found that large loads of sodium bicarbonate failed to produce sustained alkalosis in the presence of an adequate intake of potassium and adequate output of urine.

The following series of experiments was designed to study in quantitative fashion the role of potassium in the prevention of alkalosis.

EFFECTS OF POTASSIUM INTAKE IN MODIFYING THE METABOLIC ADJUSTMENT TO LOADS OF SODIUM BICARBONATE

Plan of Experiments and Methods. Groups of six male albino rats, weighing 200 to 300 gm., were fed a low electrolyte diet. This diet which contains negligible amounts of sodium, potassium and chloride has been described previously.[5] Solutions of sodium, potassium, bicarbonate and chloride ions were substituted for drinking water and were the sole source of these ions. Individual intake of these solutions was accurately measured for periods of fifteen to twenty days, at which time serum and muscle analyses were carried out. The analytic methods are those which have been used previously in this laboratory.[5] The determination of tissue fat was carried out by a modification of the method of van de Kamer et al.[7] Only saponifiable lipid is determined by this method. Hence the tissue analyses are 2 to 3 per cent lower per 100 gm. of fat-free solids than when total lipids are determined.

Results. The results of these experiments are given in Table I. The composition of the drinking solutions is given as well as the serum and muscle composition of each group after two to three

* From the Departments of Pediatrics and Physiology of the Yale University School of Medicine, New Haven, Conn. Aided by grants from the James Hudson Brown Memorial Fund of the Yale University School of Medicine, the United States Public Health Service, and the Playtex Park Research Institute.

† John and Mary R. Markle Scholar in Medical Science.

weeks on this regimen. As shown in the table, the concentration of sodium bicarbonate in the solution drunk was approximately 150 mEq./L. in all groups with the exception of Group 5, while the concentration of potassium and chloride varied.

TABLE I
FIFTEEN TO TWENTY-DAY $NaHCO_3$ LOADS

Group	Drinking Solution (mEq./L.)				Amount Drunk (ml./day)	Serum (mEq./L.)		Muscle (mEq./100 gm. FFS)	
	Na	HCO_3	K	Cl		HCO_3	Cl	K	Na_i
1	150	150	10	10	31	24	101	..	....
2	150	150	5	5	25	25	100	43	4.6
3	152	150	3	5	21	34	87	35	10.5
4	153.5	150	1.5	5	25	34	88	..	....
5	30	30	1	1	40	30	95	39	7.2
6	150	153.5	5	1.5	30	30	88	41	9.7
7	150	163.5	15	1.5	31	25	98	43	4.9
8	150	126.5	1.5	25	31	31	88	39	10.3

In Groups 1 and 2 the concentration of potassium chloride in the drinking solution was 10 and 5 mM/L., respectively. Serum analyses were normal at the end of two weeks. Muscle analyses revealed low normal muscle potassium (K) and slightly elevated intracellular sodium $(Na)_i$ (43 mEq. of K per 100 gm. fat-free solids (FFS) and 4.6 mEq. for $(Na)_i$ per 100 gm. fat-free solids).

In Groups 3 and 4 the concentration of potassium in the drinking solution was 3.0 and 1.5 mEq./L., respectively and the chloride concentration was 5.0 mEq./L., the same as in group 2. Severe hypochloremic alkalosis resulted in all animals and intracellular sodium was elevated and muscle potassium decreased. This finding of low muscle potassium and high intracellular sodium was noted in every case in which alkalosis developed. Therefore no further mention of muscle composition need be given in subsequent groups.

In the aforementioned experiments large loads of sodium bicarbonate in the presence of low intake of chloride lead to alkalosis. These changes occurred when the molecular ratio of sodium to potassium in the intake was 30 or more, but they may simply be the result of a low absolute intake of potassium. In Group 5 the ratio of sodium to potassium of 30:1 was maintained but the concentration of potassium in the drinking water was reduced to 1.0 mEq./L. Hypochloremic alkalosis developed in these animals with low potassium intake even though the intake of sodium bicarbonate was only 20 per cent of that in Group 2.

In Group 6 the chloride concentration of the drinking solution was 1.5 mEq./L. as compared with a bicarbonate concentration of 153.5 mEq./L. The potassium concentration was 5.0 mEq./L. Eighty-five per cent of these animals developed extracellular hypochloremic alkalosis; the mean serum bicarbonate concentration of the group was 30 mEq./L. and the chloride was 88 mEq./L. Thus the minimal intake of potassium which prevented alkalosis when chloride was moderately plentiful (Group 2) did not prevent alkalosis when chloride was markedly restricted.

In Group 7 the chloride concentration in the drinking solution was the same as in Group 6 (1.5 mEq./L.) but the bicarbonate concentration was higher than in Group 6 (163.5 mEq./L.). The potassium concentration was increased threefold (15 mEq./L.). None of these animals developed alkalosis; the mean serum bicarbonate concentration was 25 mEq./L. and the chloride was 98 mEq./L. Thus increase in the intake of potassium prevented the development of alkalosis in rats receiving low chloride intake. Increasing the chloride intake, however, when potassium was restricted, did not prevent the development of alkalosis (Group 8).

Comments. The importance of potassium in the prevention of alkalosis is obvious from these experiments. Despite an intake of sodium bicarbonate in excess of 10 to 30 mM per kg. of body weight per day, alkalosis did not develop unless potassium deficiency was present as demonstrated by muscle analysis. Despite the large intake of fixed cation (Na) in excess of fixed anion (Cl) serum bicarbonate did not rise above 26 mEq./L. in more than 12 per cent of the animals as long as the daily intake of potassium exceeded 0.4 mEq./kg./day. (Fig. 1.)

Chloride intake was also critical, for even in those animals that ingested slightly more potassium than 0.4 mEq./kg./day alkalosis developed unless chloride intake exceeded 0.4 mEq./kg./day. (Fig. 2.)

From the comparison of Groups 6 and 7 in which chloride intake was markedly limited, it can be inferred that increased potassium intake prevents alkalosis, in part by increasing chloride conservation.

The experiments of Gardner in rats[8] and Ariel in humans[9] indicate that potassium defi-

ciency may lead to diarrheal stools which contain large quantities of chloride. In the present experiments stools remained hard and small so that stool losses of chloride were probably negligible. For this reason the conservation of chloride in these experiments is almost certainly renal.

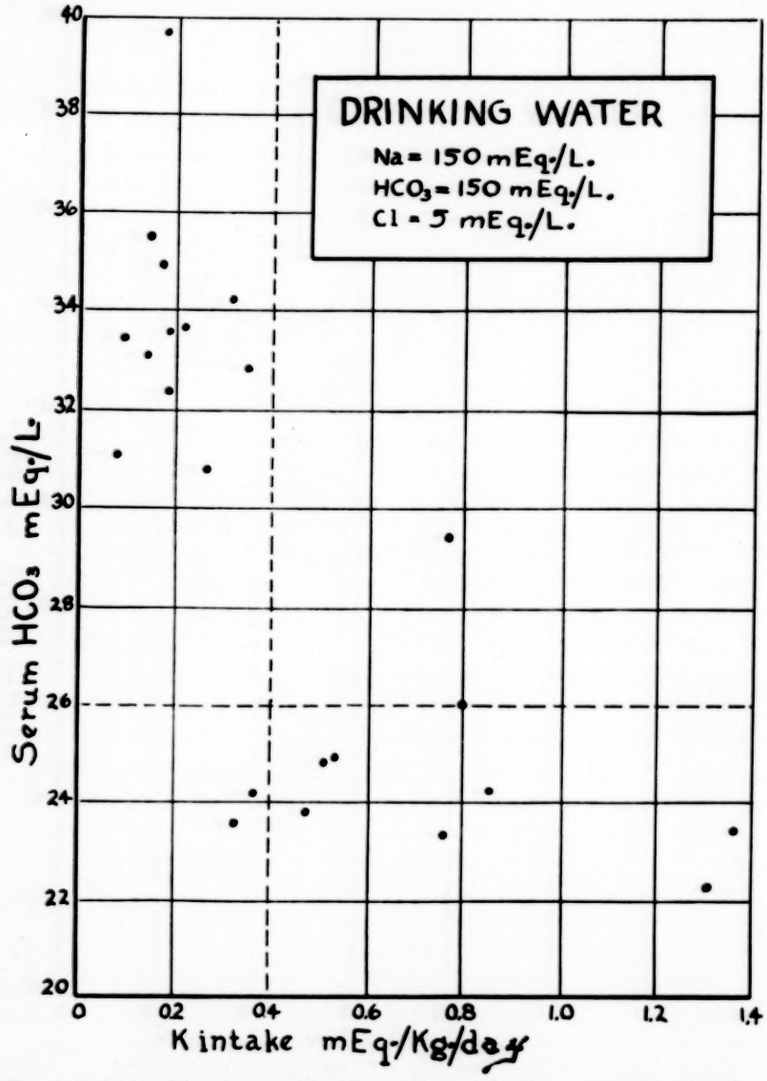

FIG. 1. Relationship of serum bicarbonate concentration to potassium intake.

In a sense, these experiments are an indirect measure of renal function even though urine is not collected. What entered the animal was accurately measured; what remained in the animal was indicated by analysis of serum and muscle which represent the major part of total body substance. Therefore, what was excreted during the experiment could be estimated by difference almost as accurately as if it had been collected and measured. This is especially true since these were long term experiments in which intake of sodium and bicarbonate was large in relation to the total quantity of these ions in the body. Since the intake of bicarbonate was fifteen to thirty times the intake of potassium over a period of fourteen to twenty-one days, it can be stated with assurance that the total amount of potassium excreted could not be equivalent to more than 3 to 7 per cent of the total bicarbonate and organic anion excreted.

The substitution of potassium in place of hydrogen in the renal tubule can therefore be of no quantitative significance in these experiments, in contrast to the findings of Berliner et al.[10] in acute experiments in dogs receiving carbonic acid inhibitor.

Nevertheless, a small intake of potassium is

necessary to meet obligatory losses of potassium and thereby prevent the development of intracellular potassium deficiency and probably intracellular acidosis. The muscle analyses indicate that muscle composition was altered in those animals in which alkalosis developed. Intracellular acidosis is associated with this type of change.[5] If analogous changes occur in the composition of the renal tubular cells, the intracellular pH probably falls, and this change may be associated with decreased reabsorption of chloride in relation to sodium. If potassium deficiency does not develop, normal intracellular composition is maintained and normal conservation of chloride in relation to sodium is maintained by the renal tubule. Conversely, if hypochloremic alkalosis develops as the result of chloride depletion or bicarbonate loading, potassium deficiency is present as demonstrated by tissue analysis.

ROLE OF POTASSIUM IN TISSUE DISTRIBUTION AND EXCRETION OF ACUTE LOADS OF SODIUM BICARBONATE

Plan of Experiment. Male albino rats, weighing 200 to 300 gm., were made potassium-deficient by a low electrolyte diet and the administration of 2 mg. of desoxycorticosterone acetate intraperitoneally daily for two weeks. A solution of sodium and ammonium chloride (NaCl = 100 mM/L. and NH_4Cl = 50 mM/L.) was substituted for drinking water during this time.

A control group of animals was fed the same diet for two weeks and a solution of sodium and potassium chloride (NaCl = 110 mM/L. and KCl = 40 mM/L.) was substituted for drinking water during this time.

The animals were then placed in individual metabolism cages and 5 per cent glucose in distilled water was substituted for the electrolyte solutions during the next eighteen hours. Nine of the potassium-deficient animals were then sacrificed. Blood was drawn from the abdominal aorta and skeletal muscle was obtained after exsanguination. The remainder of the potassium-deficient animals and all the controls were injected intraperitoneally with 15 mM of sodium bicarbonate per kg. of body weight in a volume of 150 ml. per kg. Urine was collected for the succeeding twelve hours. Serum and muscle were analyzed at the end of that time also.

Results. Serum: The mean serum analyses of the control animals were essentially normal after the load of sodium bicarbonate except for a somewhat low serum potassium and a slightly elevated pH. (Table II.) The serum bicarbonate concentration was 25 mEq./L. and the chloride concentration was 99 mEq./L.

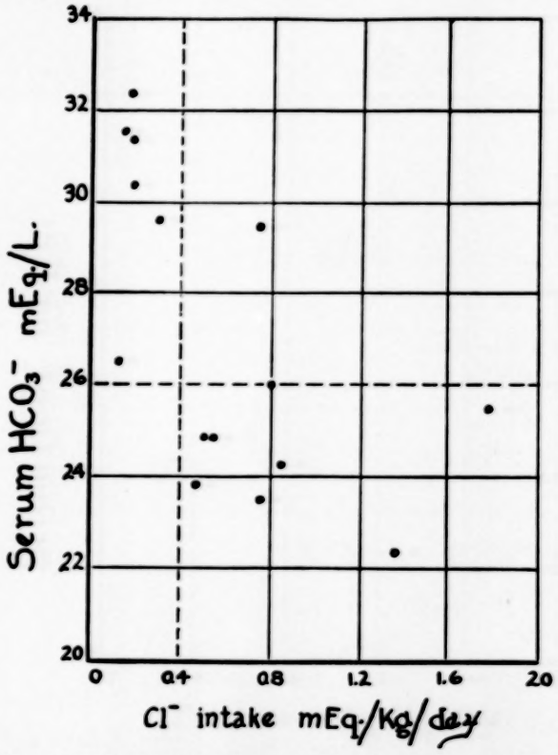

FIG. 2. Relationship of serum bicarbonate concentration to chloride intake in animals ingesting more than minimal potassium requirement. Drinking water: Na = 150 mEq./L.; HCO_3 = 150 mEq./L.; K = 5 mEq./L. (K intake > 0.4 mEq./kg./d.).

The potassium-deficient animals had moderate hypochloremic alkalosis before loading with sodium bicarbonate. The mean serum bicarbonate concentration was 28 mEq./L. and the chloride was 90 mEq./L. The serum potassium concentration was low (2.3 mEq./L.).

The concentrations of bicarbonate and chloride in the serum were grossly abnormal in the potassium-deficient group twelve hours after loading. The mean serum bicarbonate concentration was 42 mEq./L. and chloride concentration was 78 mEq./L. The serum pH rose to an average of 7.70. The differences in the serum concentrations of bicarbonate, chloride and pH between the normal and potassium-deficient animals after loading are highly significant ($p < .001$).

Serum sodium concentration did not deviate significantly from normal in either group.

Muscle: The composition of skeletal muscle was altered twelve hours after loading with sodium bicarbonate in the normal animals. (Table II.) Muscle potassium fell 5 to 6 mEq. per 100 gm. fat-free solids (FFS) from a normal value of 46 mEq./100 gm. FFS to 40 mEq./100 gm. FFS. Intracellular sodium rose about 4 mEq./100 gm. FFS from a normal value of 3.0 mEq./100 gm. FFS to 7.4 mEq./100 gm. FFS. These differences are highly significant ($p. < .001$). Muscle chloride and phosphorus did not change significantly.

In contrast with the normal animals, muscle composition did not change in the potassium-deficient group after injection of sodium bicarbonate. Muscle potassium remained at 33 mEq./100 gm. FFS and intracellular sodium remained at 12 mEq./100 gm. FFS.

TABLE II

SERUM AND MUSCLE COMPOSITION AFTER 15 MM/KG. OF $NaHCO_3$ INTRAPERITONEALLY

Group	Serum				Muscle (mEq./100 gm. FFS)		
	Cl (mEq./L.)	HCO_3 (mEq./L.)	K (mEq./L.)	pH	Cl	K	Na_i
Not K-deficient							
0 hr	100	25	4.5	7.40	5.5	46	3
12 hr	99	25	3.6	7.44	6.4	40	7.4
K-deficient							
0 hr	90	28	2.3	7.46	5.8	33	12.2
12 hr	78	42	2.4	7.70	5.2	33	12.4

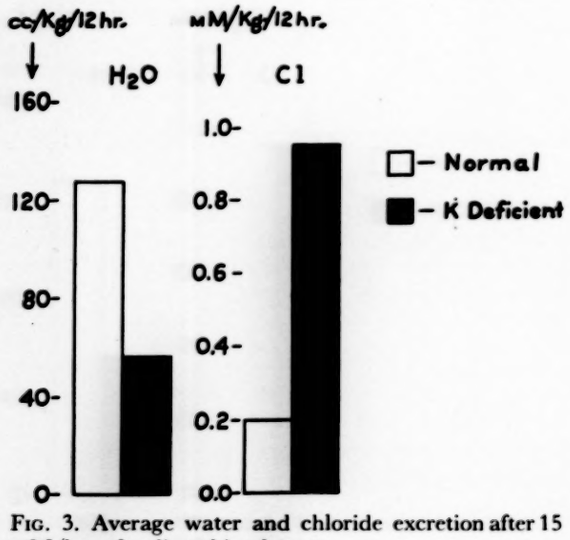

FIG. 3. Average water and chloride excretion after 15 mM/kg. of sodium bicarbonate.

Urine: The normal animals excreted approximately 90 per cent of the administered load of water (150 ml./kg.) in twelve hours and about 45 per cent of the injected bicarbonate (15 mM/kg.). (Figs. 3 and 4.) These rats excreted 15 to 16 mEq. of cation per kg. of body weight, which was equal to the administered cation load. Potassium made up 5 mEq. per kg. of the excreted cation; the balance was sodium. (Fig. 4.) The excretion of ammonia was negligible. The normal animals excreted almost no chloride (0.2 mEq./kg.) but excreted 1.4 mM/kg of phosphorus in the twelve-hour period.

The potassium-deficient animals excreted approximately 30 per cent of the administered load of water in twelve hours and about 15 per cent of the bicarbonate injected. Ascites was observed grossly in some of these animals. These rats excreted only 6.0 mEq. of cation per kg. of body weight, 99 per cent of which was sodium. The potassium excretion was less than 0.1 mEq./kg., as was the ammonia excretion. The striking finding was the excretion of chloride which amounted to 0.9 mEq./kg., roughly four and a half times the chloride excretion in the normal animals despite a low serum chloride in the potassium-deficient group at the beginning of the experiment. The excretion of phosphorus was 0.5 mM/kg.

The differences in excretion of water, sodium, potassium, bicarbonate, chloride and phosphorus

between the normal and potassium-deficient animals are highly significant ($p < .001$).

Comments. In response to acute loads of sodium bicarbonate the normal animal excretes a considerable quantity (5 mEq./kg.) of potassium. This quantity of potassium has been demonstrated in the experiment to come from skeletal muscle.

CALCULATION I

CHANGES IN DISTRIBUTION OF K

Δ K of muscle = -5 mEq./100 gm. FFS
100 gm. FFS of muscle in 1 kg. of rat
Therefore: Δ K of muscle = -5 mEq./kg. of rat

These findings indicate that a part of the potassium of skeletal muscle serves as a large quantity of cation which is readily available for excretion.

Whether the initial step in metabolic readjustment to alkalosis is the renal excretion of extracellular potassium with subsequent movement of potassium from muscle cells, or whether the initial step is movement of potassium out of cells in response to elevated extracellular pH cannot be determined from this experiment. Probably both processes occur simultaneously. The data of Keating et al.[11] on nephrectomized dogs indicate that serum potassium does not rise in acute experiments after the injection of sodium bicarbonate and suggest that the initial response to alkalosis is renal excretion of potassium. However, this finding does not exclude release of cell potassium in response to alkalosis over longer periods.

The quantity of potassium which is excreted rapidly is probably the "labile potassium" of muscle described by Miller and Darrow[12] and more recently by Holliday, Wallace and Gamble.[13] These workers showed that about 8 per cent of muscle potassium, equivalent to about 4 mEq. per kg. of body weight, could be lost from muscle without obvious change in function or extracellular composition. Holliday, Wallace and Gamble concluded that, since there were no changes in extracellular concentrations, small changes in muscle potassium are not physiologically or clinically significant. The present experiments demonstrate that the "labile potassium" of muscle is apparently the first line of defense against alkalosis. By exchange of intracellular potassium for extracellular sodium and rapid excretion of the potassium, a rise in serum bicarbonate concentration is mitigated since total cation excretion is facilitated. Likewise, "labile potassium" of muscle may sustain the potassium concentration of plasma which may fall during acute loading with sodium bicarbonate because of increased renal excretion. In this way alterations in electrolyte composition within renal tubular cells may be prevented.

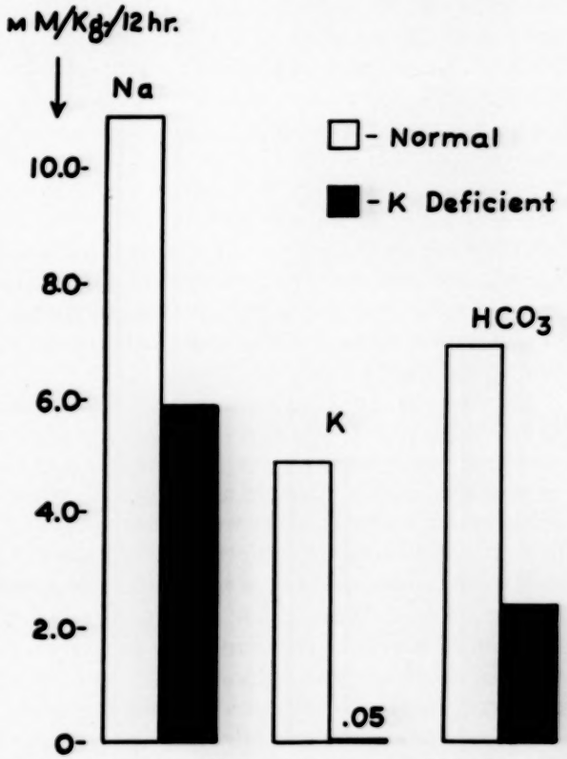

FIG. 4. Average sodium, potassium and bicarbonate excretion after 15 mM/kg. of sodium bicarbonate.

These defense mechanisms are not available after "labile potassium" has been excreted.

There is considerable evidence in the present experiments that in the presence of severe cellular potassium deficiency renal cell function is modified and chloride conservation is impaired. The mechanism of the change in renal function in potassium deficiency is not understood. Glomerular filtration rate (GFR) may be decreased in rats[14] and in humans[15] with chronic potassium deficiency. Likewise, glomerular filtration may have been impaired in the potassium-deficient animals studied in these experiments, since excretion of water and sodium after loading was considerably less than in the normal animals. Another possible explanation for the diminished water and sodium excretion is presented in the conclusion of this paper.

In the presence of a markedly decreased

filtered load, which is the result of low serum chloride concentration and possibly decreased filtration, the relatively large excretion of chloride indicates that chloride reabsorption is diminished in potassium deficiency.

It is frequently forgotten that the concentrations of sodium and chloride in tubular reabsorbate must be almost identical with their concentrations in an ultrafiltrate of plasma, since GFR is so large in relation to extracellular volume and total urinary excretion. Since fifteen times the total quantity of extracellular water and electrolyte is filtered each day in the normal animal, approximately 110 mEq. of chloride and 140 mEq. of sodium per L. of glomerular filtrate must be reabsorbed in order to maintain normal extracellular composition. If, for example, 130 mEq. of chloride were reabsorbed per L. of glomerular filtrate, serum chloride concentration would rise to that level in a few hours.

Likewise, in the potassium-deficient animal 80 to 100 mEq. of chloride and 140 mEq. of sodium per L. of glomerular filtrate must be reabsorbed or else low serum chloride and elevated serum bicarbonate concentration would not persist. A low concentration of chloride in relation to sodium in plasma and hence in tubular reabsorbate is also characteristic of compensated respiratory acidosis. This similarity in reabsorption of sodium and chloride in potassium deficiency and in respiratory acidosis suggests a similar change in the cells effecting this reabsorption. In respiratory acidosis there is an intracellular acidosis since carbon dioxide tension is elevated in all body fluids. Likewise, potassium deficiency leads to increased acidity in muscle cells.[5,16] It is likely that the acidity of renal tubular cells is increased in potassium deficiency as well as in respiratory acidosis and that it is the acidity of these cells which controls the relative amounts of sodium and chloride reabsorbed from glomerular filtrate.

This experiment raises one point of importance in practical fluid therapy. Numerous formulas have been used to calculate the dose of sodium bicarbonate necessary to raise the serum bicarbonate concentration a given amount. In this experiment the same dose of sodium bicarbonate produced no rise in serum bicarbonate concentration after twelve hours in normal animals but produced severe alkalosis in potassium-deficient animals. Therefore, unless intracellular composition is known (and this is impossible clinically), calculation of sodium bicarbonate dosage from formulas cannot be done with any degree of accuracy. Consequently sodium bicarbonate or lactate must be administered in small doses on a trial and error basis, with frequent analysis of serum concentration as a guide to alkali therapy. In addition, correction of deficits of intracellular ions must also be carried out.

CORRECTION OF ALKALOSIS WITH POTASSIUM BICARBONATE

Plan of Experiment. This experiment consisted of the determination of the composition of serum, muscle and urine during the administration of potassium bicarbonate to deficient rats in the same manner as reported previously during the correction of alkalosis with potassium chloride.[5]

Male albino rats, weighing 250 to 300 gm., were made alkalotic and potassium-deficient in the course of three weeks by the feeding of a low electrolyte diet and the intraperitoneal injection of 2 mg. of desoxycorticosterone acetate (DCA) daily. An isotonic solution of sodium chloride and sodium bicarbonate in a molecular ratio of 2.0:1.0 was substituted for drinking water.

These animals were then transferred to individual metabolism cages. Distilled water was substituted for the salt solution. DCA injections were discontinued but the diet was not modified. After two days a control urine was collected for forty-eight hours. Potassium bicarbonate, 3 mM/kg. of body weight, was then injected intraperitoneally twice daily in a hypotonic solution (100 mM/L.). No sodium or chloride whatsoever was administered for the remainder of the experiment.

All cages, screens and funnels were treated with a silicone to facilitate rapid and complete drainage. All urine was collected under mineral oil and thymol was used as a preservative. Feces were excluded from urine but were not analyzed.

Other animals were treated similarly except that urine was not collected. These animals were killed at the beginning of and at appropriate intervals throughout the experiment. Analyses of blood drawn from the abdominal aorta during pentobarbital anesthesia and of muscle were obtained on these animals as well as those studied in metabolism cages.

Results. Serum: There was progressive correction of the extracellular hypochloremic alkalosis during the course of the experiment. (Table III.) Five of the eight animals were completely corrected at the end of the experiment and these animals are grouped separately in

Table III. Serum bicarbonate concentration fell from a mean of 33 mEq./L. to 26 mEq./L. after the administration of 24 mM/kg. of potassium bicarbonate in four days. Serum chloride concentration rose progressively from a mean of 84 mEq./L. to 97 mEq./L. by the end of the experiment. Serum potassium concentration rose to normal levels and serum sodium remained at normal levels during the experiment. The changes in serum bicarbonate and chloride and potassium concentrations between the beginning and end of the experiment are statistically significant ($p < .01$).

TABLE III

AVERAGE SERUM CONCENTRATIONS

(TREATED ANIMALS RECEIVED 3 mM/KG. OF $KHCO_3$ B.I.D.)

Group	No.	Days	Na (mEq./L.)	K (mEq./L.)	Cl (mEq./L.)	HCO_3 (mEq./L.)
Normal	..	..	143	5.0	100	24
K-deficient	4	0	142 ± 6	2.2 ± 0.2	84 ± 2	33 ± 3
$KHCO_3$ 6 mM	4	1	145 ± 4	3.1 ± 0.1	91 ± 2	34 ± 2
$KHCO_3$ 12 mM	4	2	143 ± 1	3.7 ± 0.2	93 ± 1	28 ± 2
$KHCO_3$ 18 mM	4	3	144 ± 2	4.0 ± 0.4	99 ± 1	27 ± 2
$KHCO_3$ 24 mM	8	4	142 ± 3	4.2 ± 0.7	97 ± 5	26 ± 5
Completely Corrected Animals						
$KHCO_3$ 24 mM	5	4	142	4.5	101	23.5

TABLE IV

AVERAGE MUSCLE COMPOSITION PER 100 GM. FAT-FREE SOLIDS

(TREATED ANIMALS RECEIVED 3 mM/KG. OF $KHCO_3$ B.I.D.)

Group	No.	H_2O	Cl	Na	K	Na_i
Normal	..	340	5.5	10.0	46	3
K-deficient	4	323 ± 3	5.0 ± 0.4	19.5 ± 2.0	28.8 ± 1.8	13.5 ± 1.5
$KHCO_3$ 6 mM/kg	4	326 ± 2	5.0 ± 0.3	16.0 ± 1.8	35.8 ± 1.9	9.5 ± 1.5
$KHCO_3$ 12 mM/kg	4	326 ± 7	5.0 ± 0.6	13.5 ± 1.7	38.0 ± 1.6	7.8 ± 0.6
$KHCO_3$ 18 mM/kg	4	325 ± 4	5.1 ± 1.3	12.8 ± 2.2	40.0 ± 3.1	7.5 ± 1.8
$KHCO_3$ 24 mM/kg	8	317 ± 10	5.0 ± 0.5	11.8 ± 2.4	41.3 ± 3.3	6.5 ± 2.5
Completely Corrected Animals						
$KHCO_3$ 24 mM/kg	5	320	5.0	10	43.5	4.5

Muscle: Muscle composition returned toward normal after 24 mM of potassium bicarbonate per kg. had been injected. (Table IV.) The animals had a very low muscle potassium (29 mEq./100 gm. FFS) and an elevated intracellular sodium (13.5 mEq./100 gm. FFS) before injection of potassium bicarbonate. The potassium content rose to low normal levels and intracellular sodium fell during correction. In the completely corrected animals muscle potassium rose to 43.5 mEq./100 gm. FFS (low normal). Intracellular sodium fell to 4.5 mEq./100 gm. FFS. Muscle chloride and water did not change significantly during the experiment. The changes in muscle potassium and intracellular sodium between the beginning and end of the experiment are statistically significant ($p < .01$).

Urine: The daily excretion of sodium increased until 12 mM of potassium bicarbonate per kg. had been injected, even though no sodium was being administered. Sodium excretion then gradually diminished. (Fig. 5.) Water excretion increased in a parallel fashion and body weight

was approximately 10 per cent less at the end of the experiment than at the beginning.

The excretion of potassium was low for the first two days after injections of potassium bicarbonate were begun and then increased to approximately the quantity injected each day by the end of the experiment. (Fig. 5.) The ammonia excretion fell throughout the course of the experiment. (Fig. 5.)

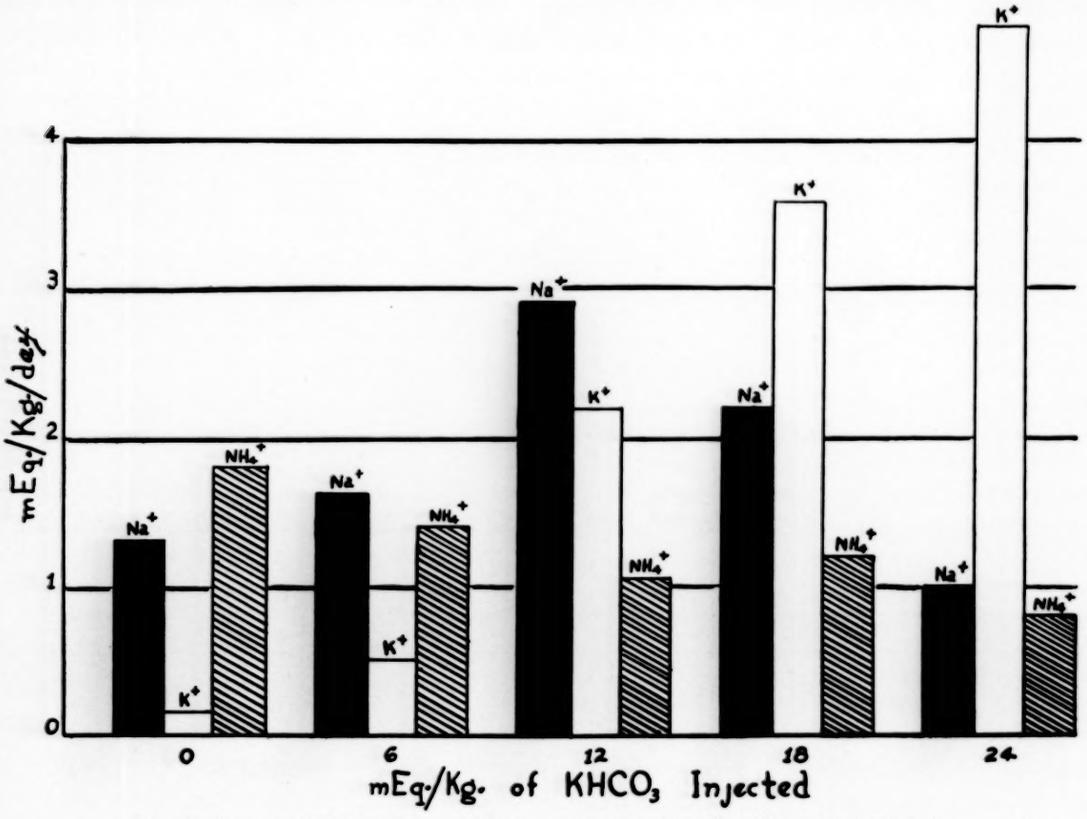

FIG. 5. Average daily cation excretion in potassium bicarbonate treated animals.

Even though extracellular alkalosis was corrected by the administration of alkali (potassium bicarbonate), urine pH and titratable acidity remained relatively constant throughout the whole experiment. (Fig. 6.) Likewise, urinary bicarbonate excretion rose only slightly despite the administration of potassium bicarbonate. (Fig. 7.) Phosphorus excretion did not change significantly and was negligible.

The cumulative balance of sodium, potassium and chloride revealed an increase in body potassium greater than the loss of sodium. Body chloride changed relatively little. (Fig. 8.)

Sodium and potassium were excreted largely with organic anion as the experiment progressed. (Fig. 7.) This quantity of organic anion was calculated as the difference between the sum of urinary sodium, potassium and ammonium ions and the sum of chloride, bicarbonate and phosphorus. These high values for organic anion were confirmed for the last four days of the experiment by titration between pH 8.0 and 3.0 after removal of phosphate with calcium oxide according to the method of Van Slyke and Palmer.[17] Part of this organic anion was probably citrate* which represented 2 per cent of the organic anion at the beginning of the correction of potassium deficiency and rose to 35 per cent of the undetermined anion by the end of the experiment. There was an absolute increase of fifty to a hundred fold in the excretion of tricarboxylic acid during the correction of potassium deficiency. The balance of the organic anion was not identified. Qualitative tests demonstrated that it was not acetone bodies.

Comments. The correction of metabolic alkalosis associated with potassium deficiency by

* We are indebted to Dr. Irving Sherman of the Department of Physiology, Yale University School of Medicine, for the citrate analyses according to the method of Saffran and Denstedt[18] which is specific for tricarboxylic acids.

KCl and by $KHCO_3$ presents certain differences, although the effect on renal function may be essentially the same. When KCl is administered, the exchange between extracellular and intracellular fluid may be represented as follows: (1) three KCl are added to extracellular fluid; (2) three K enter the cells in exchange for two Na and one H. This exchange leaves extracellular fluid with three NaCl, one of which is formed by the reaction of H and Cl with $NaHCO_3$. The fall in bicarbonate concentration when KCl is given therefore does not depend primarily on the kidneys.

When $KHCO_3$ is administered, the reactions

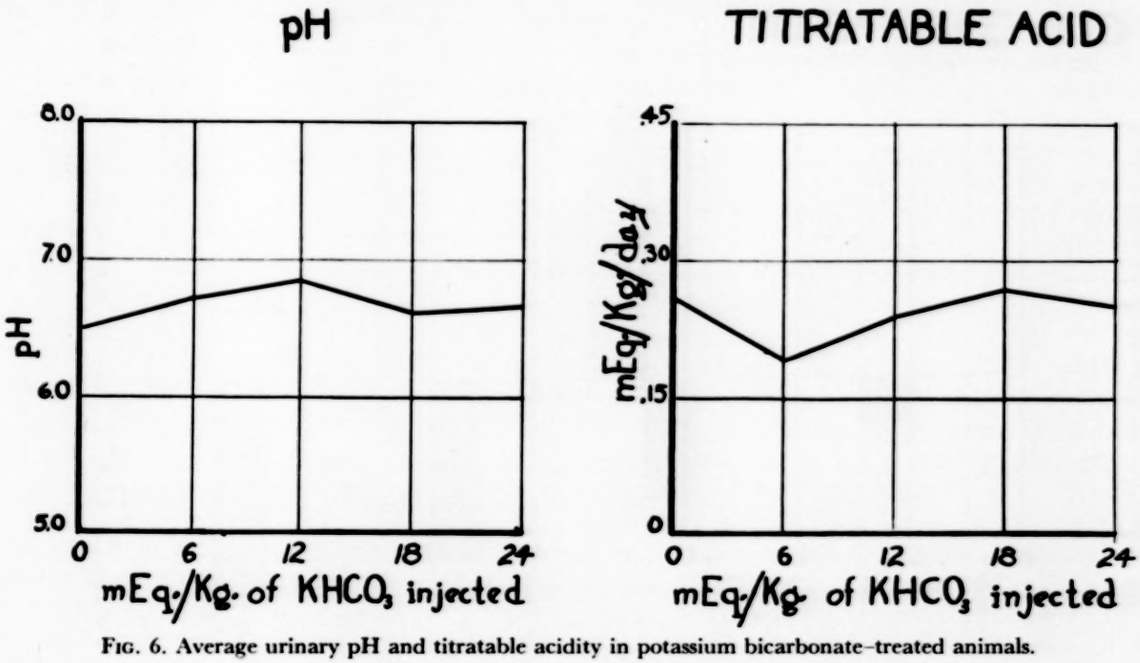

FIG. 6. Average urinary pH and titratable acidity in potassium bicarbonate–treated animals.

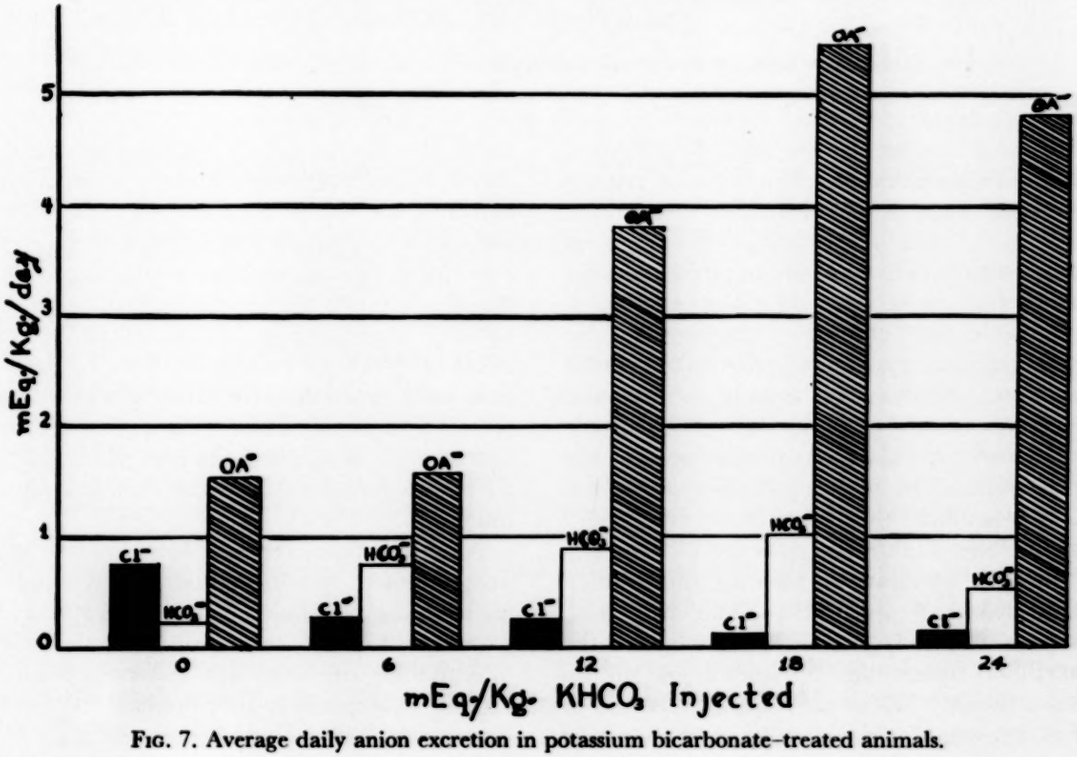

FIG. 7. Average daily anion excretion in potassium bicarbonate–treated animals.

are as follows: (1) three $KHCO_3$ are added to extracellular fluid; (2) three K enter the cells in exchange for two Na and one H. This exchange leaves extracellular fluid with two additional $NaHCO_3$. The H reacts with one administered HCO_3 to form CO_2. The administration of $KHCO_3$ would raise extracellular $NaHCO_3$ if the kidneys did not excrete Na. Thus correction of alkalosis with $KHCO_3$ must be of renal origin.

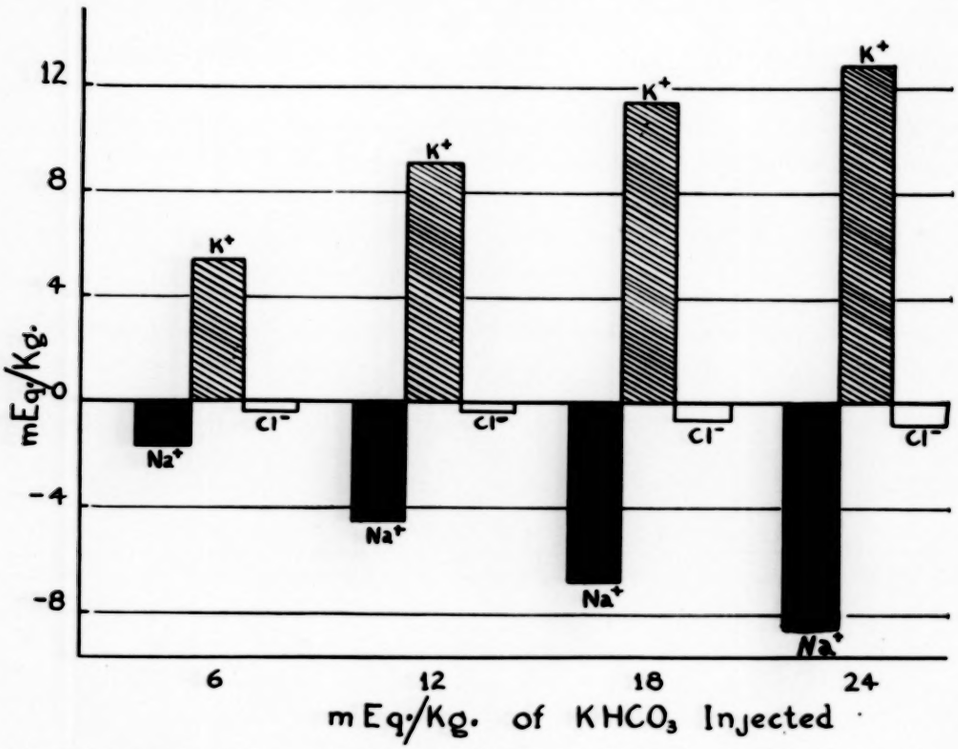

FIG. 8. Cumulative balance of sodium, potassium and chloride in potassium bicarbonate-treated animals.

The correction of hypochloremia in the present experiment can be accounted for in several ways. It is possible that chloride from intracellular stores might have exchanged with extracellular bicarbonate. Analysis of muscle before and after correction revealed no change in muscle chloride, thereby ruling out muscle cells as the source of significant amounts of chloride. Moreover, it is unlikely that other body cells could contribute the amount of chloride (3.0 mEq./kg.) which is necessary to raise serum chloride concentration 15 mEq./L., since the total chloride of the body outside of muscle and the extracellular space as measured by inulin amounts to only 5.0 or so mEq./kg. A loss of 3 mEq./kg. would mean a 60 per cent reduction in the quantity of chloride. Furthermore, if chloride of other cells behaves like red cell chloride, intracellular chloride would tend to increase rather than decrease during the experiment, since extracellular alkalosis was corrected.

If chloride was not added to extracellular fluid, the rise in serum chloride concentration can only be accounted for by a reduction in extracellular volume. The magnitude of the reduction in extracellular volume required to produce such a rise in chloride concentration is on the order of 12 per cent. Reduction in extracellular volume was accomplished either by renal excretion or transfer of extracellular water into cells, or both. The mean changes in body weight which were observed are consistent with a loss of water from the body as a whole, although there was considerable variation from animal to animal.

Any reduction in extracellular volume must be accompanied by a loss of extracellular sodium if serum sodium remains constant, as it did in this experiment.

Although the data are not completely consistent, it is possible to calculate the probable changes in distribution of body sodium.

CALCULATION II

CHANGES IN DISTRIBUTION OF SODIUM PER KG. OF BODY WEIGHT

$(H_2O)^*_{e1}$ = 200 ml. (assumed)

$(Cl)_1$ = $[Cl]_1 \times (H_2O)_{e1}$ = 18.8 mEq.

$(Cl)_2$ = $(Cl)_1 - \Delta(Cl)_{total}$ = 18.4 mEq.

$(H_2O)_{e2} = \frac{(Cl)_2}{[Cl]_2}$ = 170 ml.

$(Na)_{e1}$ = $(H_2O)_{e1} \times [Na]_1$ = 28.4 mEq.

$(Na)_{e2}$ = $(H_2O)_{e2} \times [Na]_2$ = 24.2 mEq.

$\Delta(Na)_e$ = $(Na)_{e1} - (Na)_{e2}$ = −4.2 mEq.

$\Delta(Na)_i$ (from muscle analysis) = −7.0 mEq./100 gm. FFS

Theoretical $\Delta(Na)_{total} = \Delta(Na)_e + \Delta(Na)_i$ = −11.2 mEq.

Actual $\Delta(Na)_{total}$ (urine) = −8.4 mEq.

* ( ) refers to the total amount in mEq.

[ ] refers to concentration in ultrafiltrate of serum in mEq. per gm. of water.

(H_2O) refers to volume of fluid in ml.

FFS refers to fat-free solids of muscle in grams and equaled 100 gm./kg. of rat.

Subscripts "e" and "i" refer to extracellular and intracellular, respectively.

Subscripts "1" and "2" refer to values before and after correction, respectively.

These calculations indicate that somewhat more sodium was lost from extracellular fluid and muscle than was accounted for in the urine. Unquestionably, some errors occur in collections and these would be in the direction of reducing excretion. However, the balance of potassium, 13 mEq. per kg., which also depends on excretion, agrees well with the observed increase in muscle potassium, 12.5 mEq. per kg. of body weight. Therefore, errors in collection are probably not large.

Other errors in such calculations can arise from irregular sampling, since relatively small groups of animals are used and standard deviations from the mean are large. The standard deviations of intracellular sodium do not permit a calculation of loss of intracellular sodium closer than ±2.5 mEq./kg. The urinary balances have a similar uncertainty.

It is possible that some sodium may have been adsorbed on bone during correction. No data are available which can confirm or deny this possibility. The experiments of Wallace[19] indicate that the sodium content of bone falls rather than rises as serum pH and bicarbonate decrease.

Whether change in bone sodium or shift of chloride from cells occurred during correction, a large part of the rise in serum chloride concentration was the result of a reduction in extracellular volume. The probable mechanism for this reduction is discussed in the conclusions of this paper.

A remarkable finding in this experiment was the magnitude of the excretion of organic anion during administration of potassium bicarbonate. The excretion of organic anion permitted the excretion of sodium and potassium in excess of chloride without marked rise in urine pH or urinary bicarbonate concentration.

In 1931 Oestberg[20] demonstrated that urinary citrate excretion was increased in alkalosis. Sherman et al.[21] confirmed these findings. These workers related increased citrate excretion to increased urinary alkalinity. In the present experiment citrate excretion increased markedly after the administration of potassium bicarbonate even though urine pH did not rise. Hence increased citrate excretion is not a consequence of greater urinary alkalinity.

The organic anion demonstrated in this study may originate in tissue cells such as liver or muscle because citrate is a metabolite of all cells. Furthermore, it is known that potassium influences carbohydrate metabolism in tissues.[22] However, previous work[21] showing a rise in urinary citrate following administration of sodium bicarbonate did not show high blood citrate as would be expected if increased excretion was the result of greater production in muscle and liver.

It seems more likely that in the presence of adequate potassium, renal tubular citrate metabolism is accelerated. Thus organic anion from renal tubular cells may be exchanged for chloride which is filtered, in the renal defense against alkalosis, just as ammonium ion is exchanged for sodium in the renal defense against acidosis. (Fig. 9.) Further studies are necessary to determine the exact nature and source of the organic anion observed in this experiment.

CONCLUSIONS FROM THESE EXPERIMENTS

The results of these experiments illustrate an old but important concept in the understanding of acid-base balance of the body. Although the concentrations of bicarbonate and carbonic acid are the immediate physicochemical determinants of the pH of extracellular fluid, the long range acid-base status of the body is determined by the relation of the principal fixed cations of the body (Na and K) to the principal fixed anions (Cl and P). Respiratory mechanisms alter the carbon dioxide tension (carbonic acid

concentration) in all body tissues and are, therefore, one factor that determines extracellular and intracellular pH. The bicarbonate concentration of extracellular fluids is, mainly, dependent on the concentration of sodium in relation to chloride, except for minor fluctuations in this compartment. The body as a whole retained fixed cation in excess of fixed anion during the correction, demonstrating that a cation deficit was actually present at the beginning of the experiment despite extracellular alkalosis.

Likewise, renal regulation of acid-base balance may be considered in terms of the excretion and conservation of fixed cations and anions rather than in terms of the excretion or reabsorption of hydrogen ions or bicarbonate ions, since essentially limitless quantities of hydrogen and bicarbonate ions are available from renal cellular metabolism. In general, then, renal function may be seen to involve primarily the conservation (reabsorption) of extracellular materials (sodium, chloride, glucose, etc.) and excretion (filtration and secretion) of materials of intracellular origin (potassium, phosphorus, etc.).

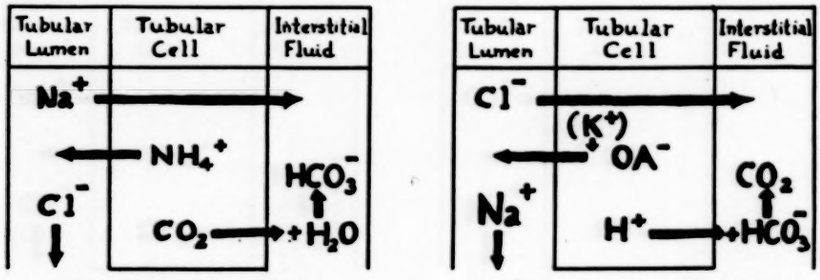

FIG. 9. Renal tubular transfer probably present in acidosis and alkalosis.

protein concentration and variations in concentration of organic acids which may be metabolized to form bicarbonate.

Although the concentration of carbon dioxide and hydrogen ion is small in body fluids at a given moment, there is an almost infinite quantity of these materials available in the living organism since intracellular metabolic processes are continuously producing carbon dioxide or hydrogen ions or both by the following reactions:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$
$$CHO \rightarrow H^+ + Anion^-$$

For this reason the acid-base balance of the body as a whole cannot be described in terms of the balance of hydrogen ions or bicarbonate ions. Rather, the balance of the fixed cations (sodium and potassium) and the fixed anions (chloride and phosphorus) determine the amount of bicarbonate (or potential bicarbonate, such as lactate and pyruvate) in body fluids.

Since the present studies show no significant change in total body phosphorus, the acid-base equilibrium was determined by the balance of sodium, potassium and chloride. The correction of alkalosis associated with potassium deficiency by the administration of potassium bicarbonate in the presence of acid urine is not readily accounted for in terms of the balance of hydrogen or bicarbonate ions. Such a correction is understandable, however, in terms of the balance of sodium, potassium and chloride. There was a loss of sodium in excess of chloride from extracellular fluid and there was a gain of potassium in intracellular fluid greater than the loss of sodium from

As was discussed earlier in the paper, extracellular composition is established and maintained by the ratio of sodium to chloride in the renal tubular reabsorbate since filtration of these substances is many-fold greater than the intake or excretion of these substances. The first two experiments of this study indicate that potassium deficiency alters the ratio of sodium to chloride in the reabsorbate and hence leads to extracellular hypochloremic alkalosis. The third experiment (the correction of alkalosis with potassium bicarbonate) indicates that the *volume* of extracellular fluid as well as the *concentration* of ions in extracellular fluid may be altered by intake of potassium.

For many years Gamble[23] and Peters[24] have emphasized the phenomenon of preservation of extracellular concentration at the expense of extracellular volume. The present experiments indicate that normal extracellular concentration of bicarbonate and chloride is restored at the expense of a decrease in extracellular volume when abundant potassium is present and external

sources of sodium and chloride are not available. On the other hand, when potassium deficiency is present, serum bicarbonate remains high, even when sodium chloride is administered, and extracellular volume increases. These findings can be reconciled by assuming that an intake of potassium which is adequate to maintain normal intracellular composition permits reabsorption of sodium and chloride in the normal ratio from glomerular filtrate. In the presence of hypochloremic alkalosis reabsorption of sodium and chloride in a normal ratio leads to increased excretion of sodium and extracellular water as demonstrated by the following hypothetic calculations:

CALCULATION III

CORRECTION OF K DEFICIENCY PER 1 L. OF GLOMERULAR FILTRATE

[Na]* filtered = 140 mEq./L.
[Cl] filtered = 100 mEq./L.
(Na)* filtered = 140 mEq.
(Cl) filtered = 100 mEq.

Normal reabsorbate ratio $= \frac{[Na]}{[Cl]} = \frac{140}{110}$

Assuming maximal possible reabsorption of Cl (100%)†

(Cl) reabsorbed = 100 mEq.
[Cl] reabsorbate = 100 mEq./L.
(H_2O) reabsorbed $= \frac{100}{110} \times 1000$
$= 909$ ml.
[Na] reabsorbate = 140 mEq./L.
(Na) reabsorbed $= 140 \times .909$
$= 127$ mEq.
(H_2O) excreted $= 1{,}000 - 909$
$= 91$ ml.
(Na) excreted $= 140 - 127$
$= 13$ mEq.
(Cl) excreted $= 100 - 100$
$= 0$ mEq.

*[ ] and ( ) refer to concentration and total amount, respectively.

† If less than 100 per cent of filtered Cl is reabsorbed, then even greater loss of Na and H_2O will occur.

These calculations indicate a large loss of water and sodium from each liter of glomerular filtrate with resulting decrease in extracellular volume when the normal ratio of sodium to chloride in the reabsorbate is restored. Obviously this correction of reabsorbate composition is not an instantaneous event, as is implied in these calculations, but occurs in a stepwise fashion as intracellular potassium is restored. The calculations represent only the end result of a continuing series of events. When normal serum concentration of sodium and chloride is finally restored, a new equilibrium is then established with preservation of the existing extracellular volume and concentrations. The mechanisms whereby the ratio of Na to Cl in the reabsorbate is maintained are obviously complex. The present discussion is simply a description of the end results and somewhat resembles the original description of renal function by Cushny in 1926.[25]

The development of expanded extracellular volume, which is stated to be an early sign of potassium deficiency,[26] can be explained in a similar fashion if it is assumed that the ratio of sodium to chloride in the reabsorbate is altered in potassium deficiency. The evidence for such an alteration has been presented in the comments on the previous experiments. The following hypothetic calculations demonstrate the retention of sodium and water resulting from potassium deficiency:

CALCULATION IV

DEVELOPMENT OF K DEFICIENCY PER 1 L. OF GLOMERULAR FILTRATE

[Na]* filtered = 140 mEq./L.
[Cl] filtered = 110 mEq./L.
(Na)* filtered = 140 mEq.
(Cl) filtered = 110 mEq.

Altered reabsorbate ratio $= \frac{[Na]}{[Cl]} = \frac{140}{100}$

Assuming maximal possible reabsorption of Cl (91%)†

(Cl) reabsorbed = 100 mEq.
[Cl] reabsorbate = 100 mEq./L.
(H_2O) reabsorbed $= \frac{100}{100} \times 1{,}000 = 1{,}000$ ml.
[Na] reabsorbate = 140 mEq./L.
(Na) reabsorbed $= 140 \times 1{,}000 = 140$ mEq.
H_2O excreted $= 1{,}000 - 1{,}000 = 0$ ml.
(Na) excreted $= 140 - 140 = 0$ mEq.
(Cl) excreted $= 110 - 100 = 10$ mEq.

*[ ] and ( ) refer to concentration and total amount, respectively.

† If greater than 91 per cent of filtered chloride is assumed to be reabsorbed, more sodium and water than is filtered would have to be reabsorbed. Such a situation would obviously be impossible.

These calculations indicate a marked conservation of sodium and water (100 per cent) from each liter of glomerular filtrate with resulting expansion of extracellular volume if saline solution is administered. Such a readjustment in volume and concentration will continue until a new equilibrium is established.

Such a disturbance in the ratio in which sodium and chloride are reabsorbed from glomerular filtrate may well be responsible for the refractoriness of some cases of cardiac edema to mercurial diuretics. Pitts[27] noted little natriuretic response to mercury in respiratory acidosis, a condition analogous to potassium deficiency from the standpoint of these calculations.

If Calculations III and IV are compared, it can be seen that in the correction of potassium deficiency (Calculation III) essentially no chloride is excreted and yet extracellular volume is decreased. Conversely, in the development of potassium deficiency (Calculation IV) there is diminished chloride conservation and yet extracellular volume is expanded. Thus the apparent paradox of chloride wasting associated with expansion of extracellular volume in potassium deficiency can be explained in this way.

The finding of Schwartz et al.[28] that whole body chloride is not diminished in rats made potassium-deficient by low potassium, high sodium chloride diet is compatible with the concept presented herein. If intake of chloride is high, the content of chloride in the body as a whole will be maintained even though chloride is excreted when serum concentrations are low. However, total body chloride can be normal only if extracellular volume and extracellular sodium are increased.

Thus it can be seen from this analysis that the composition of cells, especially with reference to intracellular pH and potassium concentration, may influence not only extracellular concentrations but also extracellular volume.

SUMMARY

1. Loads of sodium bicarbonate were administered to normal rats in drinking water along with known amounts of potassium and chloride. Alkalosis did not develop after two weeks as long as potassium chloride intake exceeded 0.5 mM/kg./day even though sodium bicarbonate intake amounted to 10 to 30 mM/kg./day. It was not possible to produce alkalosis in this way in the absence of potassium deficiency, as demonstrated by muscle analysis.

2. Sodium bicarbonate, 15 mM per kg., was injected into normal and potassium-deficient rats, and urine was collected for the subsequent twelve hours. Serum and muscle analyses were obtained at the end of that time also. Normal animals excreted 10 mEq. of sodium and 5 mEq. of potassium per kg. of body weight in the twelve-hour period following loading. Essentially no chloride was excreted and alkalosis was not present after twelve hours. Potassium-deficient animals excreted only 6 mEq. of sodium per kg. and no potassium. Almost 1 mEq. of chloride per kg. of body weight was excreted by the potassium-deficient animals and severe hypochloremic alkalosis was present twelve hours after loading.

3. Potassium bicarbonate, 3 mM per kg., was injected twice a day into potassium-deficient rats with hypochloremic alkalosis. No sodium or chloride was administered. After 24 mM per kg. of potassium bicarbonate had been administered, serum bicarbonate concentration fell to normal and serum chloride concentration rose to normal. This correction was associated with relatively little increase in bicarbonate excretion and with essentially no change in urinary pH or titratable acidity. Cation was excreted with organic anion, a large part of which was shown to be citrate.

These results suggest that citrate may be substituted for chloride in the renal defense against alkalosis so that sodium is excreted without chloride and without change in urinary pH. Potassium would seem to be essential for the maximal conservation of chloride in this way.

4. These findings suggest that potassium deficiency may alter the ratio in which sodium and chloride are reabsorbed from glomerular filtrate. Such an alteration leads to changes not only in extracellular concentrations but also in extracellular volume.

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Dehydration with Hypernatremia, Hyperchloremia and Azotemia Complicating Nasogastric Tube Feeding*

FRANK L. ENGEL, M.D. *and* CARL JAEGER, M.D.
Durham, North Carolina

WELT and his collaborators[1] have recently called attention to the occurrence of hypernatremia and hyperchloremia as manifestations of dehydration in the unconscious or debilitated patient who cannot make known or take care of his fluid requirements by himself. Normally, the sensation of thirst serves as a very adequate guide for water intake; but when this sensation cannot be experienced, as in the unconscious patient, or cannot be acted upon, as in the debilitated patient, serious discrepancies in fluid and electrolyte balance may ensue. In their report Welt et al. described several types of dehydration associated with hyperosmolarity. These were: (1) Simple dehydration in which water requirements are not unusual but are not met adequately because of failure of the patient's attendants to supply fluids adequately. (2) Dehydration secondary to unusual demands for water because of failure of the hypothalamic posterior hypophyseal system to control renal tubular reabsorption of water, i.e., diabetes insipidus. Dehydration and hypernatremia will ensue when the patient is unconscious and cannot exhibit thirst or, as in the recent case of Engstrom and Liebman,[2] when a hypothalamic lesion seemingly interferes with the normal thirst mechanisms so that polyuria exceeds polydipsia. (3) Dehydration secondary to unusual demands for fluids because of an abnormally high solute load to be excreted by the kidney. This is the situation in the unconscious patient who is fed by gavage a diet containing considerable amounts of protein without a quantity of water adequate to excrete the nitrogen from the diet. The tendency to develop such dehydration will be accentuated if the patient is in negative nitrogen balance, as he is likely to be if ill or if any degree of renal insufficiency exists and prevents the excretion of urine of maximal specific gravity. Normally the body responds to restriction of fluid intake in the face of an increased nitrogen load by excreting a urine as concentrated as possible and decreasing the excretion of sodium and chloride. Under such circumstances a comparatively large volume of urine is excreted with a high specific gravity and the serum exhibits increasing concentrations of sodium and chloride. As the process continues, azotemia may also develop. The rapidity with which hyperosmolarity develops is a function of the discrepancy between fluid intake and solute load and of the state of renal function. In patients with impaired renal function the syndrome may develop very rapidly and will be associated with considerable azotemia.

In a period of less than a year since Welt's observations came to our attention we have seen five cases of dehydration with marked hypernatremia and hyperchloremia complicating tube feeding of diets relatively high in protein to patients with impaired levels of consciousness. In each case the diet was being used routinely, often without the prescribing physician's knowledge of its actual protein content, since the diet ordered was the standard tube feeding diet in use at Duke Hospital for many years (tube feeding diet "A," Table 1). In some cases a high protein diet (tube feeding diet "B") was ordered deliberately without appreciation of the increased water requirement. The development of this syndrome generally was associated with deterioration of the clinical condition of the patient. Because of the frequency with which this syndrome has been observed in a relatively

* From the Department of Medicine, Duke University, Durham, N. C.

brief period of time with a diet comparable to that used in many hospitals and because of the potentially serious consequences of the dehydration and electrolyte disturbances resulting therefrom, it was thought desirable to record our experiences at this time.

TABLE I

NUTRITIONAL CONTENT OF TUBE FEEDING DIETS AT DUKE HOSPITAL

Tube Feeding	Calories (per cc.)	Protein (gm./1,000 cc.)	Fat (gm./1,000 cc.)	CHO (gm./1,000 cc.)	Sodium (gm./1,000 cc.)	Potassium (gm./1,000 cc.)
A	1.0	70	47	70	1.2	2.2
B	1.0	101	3	154	1.7	3.9
C	2.0	73	112	194	1.1	1.9
D	1.0	31	52	102	1.3	1.5
Rice	1.0	11	1	239	.005	1.4
Milk	0.7	35	39	40	0.5	1.4
Low Na	1.0	52	50	80	0.1	2.4

CASE REPORTS

CASE 1. M. W. (No. D-37514), age forty-five, was admitted to the Neurosurgical Service one hour following being rendered unconscious in an automobile accident. On admission he exhibited a right flaccid hemiparesis with rigidity of the left limbs, and bilaterally positive Hoffmann and Babinski responses, and ankle clonus. Bilateral temporal trepanation performed shortly after admission revealed no evidence of subdural or extradural hematomas. The blood pressure was 160/100 mm. Hg. Urine examination revealed a specific gravity of 1.026, no protein or microscopic abnormalities, but subsequently a urinary tract infection developed which responded to gantrisin® therapy. During his entire stay in the hospital he remained unconscious, responding only to painful stimuli. His course in the hospital over fourteen weeks was complicated by the development of a urinary tract infection, thrombophlebitis and drug sensitivity which accounted for a persistent fever, with temperature ranging between 38–40°C. most of the time.

On the fourth hospital day tube feeding with 2,400 ml. of tube feeding "A" (Table I) without added water was begun, and on the twentieth day this was increased to 2,700 ml. with 900 ml. of added water. The patient thus was receiving between 168 and 190 gm. of protein and 2,000–3,600 ml. of fluids per day. Intermittently during this period he received 1 L. of fluids intravenously. On the forty-third day blood chemical analyses were performed for the first time (Table II) and it was found that the serum sodium was 169 mEq./L., chloride 138 mEq./L., NPN 70 mg. per cent, total protein 8.0 gm. per cent and CO_2 combining power 31 volumes per cent. Urine specific gravity was 1.026. The low CO_2 combining power was attributed to the fact that the patient had been receiving 6 gm. of ammonium chloride because of the urinary tract infection but the hypernatremia and hyperchloremia were not explained at this time. Ammonium chloride was discontinued. Three days later the blood chemical changes were unaltered except for a rise in the CO_2 combining power. On this day the patient was seen for the first time by the present observers and the possibility of dehydration secondary to high solute intake and inadequate water intake was first suggested. Fluid intake was increased to 5,100 ml. by mouth and vein and a new diet ("D," Table I) was devised with the aid of the dietetics department and administered at a level of 2,400 ml. daily. This provided approximately 74 gm. of protein daily. Four grams of potassium as a mixture of potassium acetate, potassium bicarbonate and potassium citrate were added to the tube feeding mixture but discontinued the following day when the serum potassium rose from 3.0 to 5.9 mEq./L. Subsequently, there was a gradual return of the blood chemical findings towards normal (Table II) where they remained until the patient was discharged, still stuporous, to a nursing home.

Comment. This patient, who was previously healthy, developed hypernatremia, hyperchloremia and azotemia which was first detected forty-three days after becoming unconscious and after thirty-nine days of receiving a high protein

tube feeding. There was no evidence of previous renal insufficiency and the normal to high specific gravity of the urine indicates that there was no posterior pituitary insufficiency. On decreasing the protein and increasing the fluid intake, the hyperosmolarity and azotemia were corrected.

four hours. There was rapid deterioration in the patient's clinical state during the remainder of her stay in the hospital, with increasing stupor and unexplained temperature elevations. On the seventh day her serum chloride was 117 mEq./L. but the significance of this value was not appreciated until the eleventh day when the possibility of dehydration secondary to high protein tube feeding was first suggested. A change to a diet with less protein was advised but the patient died twenty-four hours later. Blood values on the morning of her demise showed a serum Na of 171.4 and chloride of 134 mEq./L. (Table III.)

TABLE II
CASE I

Hospital Day	43	46	47	48	49	50	52	60	67	76
Sodium (mEq./L.)	169	173.6	173.6	156.0	164.9	151.9	154.7	150.0	157.0	150.0
Chloride (mEq./L.)	138.1	135.4	134.3	136.0	125.0	114.2	119.3	105.3	107.3	104.9
CO_2 combining power (vol. %)	31	43	50	.....	64	52	55	71	68	66
Potassium (mEq./L.)	3.3	3.0	5.9	.....	5.0	4.0	2.2	4.4	4.1	3.5
NPN (mg. %)	70	78	.....	.....	80	49	31	.....	73	.....
Total protein (gm. %)	8.0	.....	.....	.....	.....	6.2	5.8	.....	.....	.....
Specific gravity urine	1.026	.....	1.014	.....	.....	.....	.....	.....	.....	.....
Fluid intake (ml.)	.....	5100	2975	3820	3300	3000	3500	3300	.....	.....
Fluid output (ml.)	.....	2400	2595	1800	1975	1725	3150	1200	.....	.....
Temperature (°C.)	39[1]	40	41	39[2]	39[3]	39	38	38[5]	39	37[5]
Diet	←"A"→		←"D"→							

CASE II. F. W. (No. A-95597), a seventy-seven year old widow, was admitted to the Medical Service with a history of sudden collapse, striking her head in the left occipital area five and one-half weeks prior to admission. Since the time of her stroke the patient had remained in bed and her course was progressively downhill with alternating periods of delirium and confusion. She had refused to eat or swallow liquids and as a consequence she became obviously dehydrated. She was known to be hypertensive for ten years. Physical examination on admission revealed a blood pressure of 180/60, pulse 44 and temperature 36.8°C. She was emaciated, dehydrated and stuporous, although she had occasional lucid intervals. There was Cheyne-Stokes respiration. The right pupil was irregular and failed to react to light. There was no papilledema. There was a flaccid left hemiparesis and 2+ pretibial edema. The urine had a specific gravity of 1.010–1.012, and showed a heavy trace of protein. The blood NPN was 100 mg. per cent and the hemoglobin 13.2 gm. Electrocardiogram revealed third degree heart block with anterior septal wall infarction and evidence of fresh anterior wall damage.

Tube feeding with diet "A" was begun the first day, the patient receiving 1,800 ml. of this diet with 1,200 ml. of extra water every twenty-

TABLE III
CASE II

Hospital Day	1	7	13
Sodium (mEq./L.)	...	.....	171.4
Chloride (mEq./L.)	...	116.9	134.0
CO_2 combining power (vol. %)	...	52	.....
Potassium (mEq./L.)	...	4.9	5.8
NPN (mg. %)	100	120	.....
Temperature (°C.)	39	39	39[5]
Diet	←"A"→		

Comment. This patient exhibited serum hyperosmolarity while receiving 120 gm. of protein and a total of 3,000 ml. of fluids per day. She had azotemia on admission and excreted a urine with maximal specific gravity of 1.012. The hypernatremia and hyperchloremia in this case probably was a consequence of simple dehydration accentuated by a comparatively

high solute load in an individual whose renal function already was impaired.

Case III. M. W. (No. 3628), a seventy-five year old man, was admitted to the Medical Service because of right frontotemporal headache and confusion of two days' duration. For the past eight years the patient had had frequent bouts of faintness, giddiness, episodes of syncope, forgetfulness, confusion and amnesia. During the three weeks before admission he had vomited several times and twitching motions of the right arm and leg were observed, although these members could be moved at will by the patient. The patient was never known to have hypertension but had had evidences of decreased renal function, as indicated by a fixed specific gravity of the urine and a low excretion of PSP. Physical examination: Blood pressure 150/80 mm. Hg, temperature 37.4°c., pulse 120, respirations 18. The patient was wiry, dehydrated, disoriented, confused and moderately combative. There were jerky tremors of the arms and legs at rest, but no abnormal reflexes were noted. The urine specific gravity ranged between 1.010 and 1.013. PSP excretion was 8 per cent in two hours.

Shortly after admission pneumonitis developed, with temperature elevation to 38–40°c. For this the patient received antibiotic therapy. Because of difficulty in feeding he was started on tube feeding "A" on the fifth day, receiving 2,000 ml. per day (140 gm. of protein) with 1,000 ml. of additional water. On that day his serum sodium was 147.8, chloride 106 mEq./L. and NPN 64 mg. per cent. (Table iv.) Following institution of tube feeding "A," his mental state deteriorated rapidly and he became stuporous. On the sixth day his NPN was 112 mg. per cent and by the eighth day it had risen to 160 mg. per cent and hypernatremia and hyperchloremia had become apparent. His diet was changed to 2,000 ml. of rice tube feeding containing 22 gm. of protein plus 800 ml. of water. With this change in protein intake, without any increase in water intake, there was gradual improvement in his clinical state and his blood electrolytes returned to normal. He became responsive and oriented and by the twenty-first day was able to feed himself.

Comment. This elderly feeble man with cerebral arteriosclerosis and renal insufficiency developed dehydration with hyperosmolarity and azotemia when given a high protein intake. The rapidity with which this developed probably represented the summation of initial simple dehydration, high protein intake, accelerated protein catabolism secondary to fever and impaired renal function. The patient's clinical condition by the eighth day was such that most observers anticipated an early demise. The correction of the hyperosmolarity and other evidences of dehydration when the patient was changed to a low protein diet without increasing the fluid intake is especially noteworthy.

Table iv
case iii

Hospital Day	5	6	7	8	14	21
Sodium (mEq./L.)	147.8	...	...	162.8	151.9	141.3
Chloride (mEq./L.)	106	...	...	121	107.3	99.8
CO_2 combining power (vol. %)	.....	...	...	49	54	.....
Potassium (mEq./L.)	4.0	...	...	4.6	3.8	4.6
NPN (mg. %)	64	112	...	160	100	70
Temperature, (°c.)	40	40	38[6]	38[8]	37[2]	37[4]
Diet	←"A"→			←Rice→		

Case iv. F. C. (No. D-53110), a forty-eight year old Negro housewife, was admitted to the Medical Service with a one-year history of nervousness, palpitation, weight loss of 100 pounds despite an increased appetite, hyperhydrosis and signs and symptoms of congestive failure. For five months there had been visible enlargement of the thyroid gland. Fourteen years previously she had had a blood pressure in excess of 200 mm. Hg during a pregnancy. Examination revealed an agitated, emaciated. dehydrated, mentally clouded woman who was obviously critically ill. Temperature was 38.2°c., pulse 120, respirations 26, blood pressure 140/60 mm. Hg. The skin was smooth and moist, the hair fine and scanty. There was a moderate stare but no lid-lag or exophthalmos. There was a marked, diffuse enlargement of the thyroid gland with a loud bruit. The heart was enlarged to the mid-axillary line, exhibiting a rapid rate with a diastolic gallop and a grade iii systolic murmur at the apex. There was hepatosplenomegaly and edema of the abdominal wall and lower extremities. A considerable degree of muscle wasting was apparent.

Laboratory findings included a hemoglobin of 8.0 gm. per 100 ml. and white blood count of 5,700 with 62 per cent polymorphonuclear leukocytes, 1 per cent eosinophils, 25 per cent lymphocytes and 12 per cent monocytes. The

urine examination was negative except for a trace of protein. Serum NPN was 34 mg. per cent, cholesterol 100 mg. per cent, bilirubin 4.4 mg. per cent, BSP 30 per cent retention in thirty minutes. The serum total protein was 8.5 gm. per cent with 2.8 gm. albumin and 5.7 gm. globulin.

TABLE V
CASE IV

Hospital Day	2	4	8	9	10
Sodium (mEq./L.)	.....	143.3	160.6	154.07	Expired
Chloride (mEq./L.)	103.9	104.6	112.8	105.6	
CO_2 combining power (vol. %)	53	59	68	80	
Potassium (mEq./L.)	.....	5.0	2.3	5.30	
NPN (mg. %)	34	.....	.....	64	
Specific gravity urine	1.011–1.013		.....	.....	
Fluid intake (ml.)	2520	5110	3610	.....	
Temperature (°c.)	38²	38²	28	37⁸	
Diet	High protein-low Na		Low protein-low Na		

The patient was judged to have thyrotoxic heart disease with thyroid crisis. Treatment with intravenous sodium iodide, methimazole® and Lugol's solution by mouth, digitoxin, mercurial diuretics, antibiotics, multiple vitamins, packed red cells and glucose in water by vein was instituted, but despite these measures her course was unfavorable. In an attempt to meet her caloric needs, 2,250 ml. of a special concentrated tube feeding containing 2 calories/ml., 200 gm. of protein and less than 200 mg. of sodium were administered daily. To combat possible secondary adrenal insufficiency 200 mg. of cortisone acetate were given daily. Despite a fluid intake between 2,500–5,110 ml./day, on the eighth day hypernatremia and hyperchloremia were noted. (Table v.) The diet was changed to one containing 70–90 gm. of protein in 2,500–3,000 ml., with 2,700 ml. of extra fluids. With this there was a significant fall in serum sodium and chloride twenty-four hours later but despite this and the other therapeutic measures the patient expired on the following day.

Comment. In this case a high protein, high calorie diet was administered deliberately by gavage to a critically ill, emaciated thyrotoxic patient in an attempt to meet her excessive caloric requirements. The need for fluid apparently exceeded that made available to her and the chemical findings of hyperosmolarity developed on the eighth day. This responded quickly to a lowering of the protein in the diet and an increase in fluids but the patient nonetheless went on to die of her disease.

CASE V. M. W. (No. D-50230), a fifty-two year old man, was admitted to the Urological Service for ureterosigmoid transplant because of contracted bladder, urethral stricture and urethrocutaneous fistulas secondary to an old gonococcal infection and much instrumentation. Two months before admission a suprapubic cystotomy had been performed. He was addicted to morphine. The blood pressure was 120/80 mm. Hg. Except for the urologic problem with multiple fistulas, there were no significant abnormalities on physical examination. Hemoglobin was 14 gm., white blood count 11,750, NPN 34 mg. per cent, PSP 65 per cent in two hours.

On the fourteenth hospital day bilateral ureterosigmoid transplant was performed under general anesthesia. The patient withstood the operative procedure well but his postoperative course was stormy. During the following two weeks he received fluids by vein as indicated in Table VI. His serum NPN rose while his serum electrolytes fluctuated with a tendency to a fall in serum potassium. On the twentieth day an emergency right pyelonephrostomy was carried out and extravasation of urine into the abdominal region was observed. Following this operation the serum NPN declined somewhat. On the twenty-seventh day tube feeding "B" was started. Between the twenty-seventh and fortieth days the diet and fluid order was changed almost daily. The protein intake ranged from 72 gm. on two days to 216 gm. for two days and 140–150 gm. the remainder of the period. Total fluid intake was of the order of 3,000 ml. per day. On the thirtieth day hypernatremia and hyperchloremia were noted but their significance was not appreciated until eight days later. (Table VI.) At that time the patient was receiving 150 gm. of protein, and the total fluid intake was increased to 4,000–6,000 ml. By the fortieth day the hyperosmolarity had been corrected and the temperature, which had been elevated during the period of dehydration, returned to normal. The serum NPN, however, remained elevated. During the next nine days the patient received rice tube feeding with 2,000–3,000 ml. of added fluids, and on this regimen his serum NaCl fell to levels somewhat below normal and his serum K rose. The serum NPN remained elevated. His course thereafter was not germane

to the problem under consideration so is not included.

Comment. Hyperosmolarity developed while the patient was receiving a high protein diet and this was corrected by increasing the fluid intake. His course was complicated by the development of a severe urinary tract infection with impaired renal function and infection secondary to urinary extravasation. The electrolyte disturbance noted in this patient should not be confused with that seen in patients with ureterosigmoid transplants in whom hyperchloremic acidosis develop without changes in serum sodium.[3] The present patient's abnormality developed at a time when urine was being drained externally through a pyelonephrostomy.

TABLE VI

CASE V

Hospital Day	2	19	22	23	28	29	30	33	38	39	40	41	45	49
Sodium (mEq./L.)	.....	143.3	151.9	150	151.9	...	162.7	161.3	164	...	147.8	147.8	....	139.1
Chloride (mEq./L.)	.....	97.4	86.5	96.1	104.6	...	111.1	122.4	123	...	102.2	104.3	90.9	88.9
CO_2 combining power (vol. %)	.....	.....	.....	64	73	...	76	77	66	...	56	65	....	65
Potassium (mEq./L.)	.....	.....	.....	3.2	3.0	...	2.6	4.4	5.3	...	5.4	4.7	....	6.1
NPN (mg. %)	34	88	155	150	90	...	76	74	75	...	110	70	56	60
Total protein (gm. %)	7.35	.....	.....	.....	.....	...	.....	.....	.....	...	6.5	.....	.....	.....
Specific gravity urine	1.010	.....	.....	1.013	.....	...	.....	.....	.....	...	.....	.....	.....	.....
Fluids	Intravenous 2,000 cc. 5% Dextrose/Water 1,000 cc. 5% Dextrose/Saline				3,000 cc. Dextrose/Water									
Diet	3 gm. KCl				←"B"→ With 1,000 cc. of water						←Rice→ With 1,000 cc. of water			
Temperature (°c.)	37	37	37	37	38	38[2]	38[4]	39	38[6]	38[2]	37[4]	37[8]	37	37

Discussion

The observation of five examples of hypernatremia and hyperchloremia in less than a year emphasizes the potential frequency of this syndrome as a complication of nasogastric tube feeding of diets comparatively high in protein. The clinical deterioration that accompanied the dehydration and hyperosmolarity in those patients in whom the primary disease was not so overwhelming as to obscure new symptoms indicates that this is a serious complication which may indeed be incriminated as a possible cause of death in some patients. With the exception of one patient who died before corrective measures could be taken, the hyperosmolarity was restored to or toward normal by either reducing the protein content of the diet or increasing the fluid intake, or both, lending credence to the interpretation that the high protein intake was an important contributing factor, if not the chief basis, for the syndrome. In most cases the physician's attention to the possibility of dehydration was clouded by the fact that the fluid intake seemed adequate by usual standards and the urine output was generous. Cognizance was usually not taken of the high insensible and extrarenal water loss exhibited by many of these patients because of fever. Nor, in general, was there appreciation of the fact that the large solute load resulting from the high protein intake accentuated renal loss of water. The latter, in turn, was exaggerated by the need to excrete extra solute because of the negative nitrogen balance which these acutely and chronically ill patients undoubtedly were exhibiting. Welt's calculation of the potential water requirement to allow for the excretion of solute loads of the magnitude to be expected in patients receiving diets of the type described in this report clearly indicates the ease with which hyperosmolarity and dehydration might develop. Thus referring to a patient who received 159 gm. of protein daily, he states "This amount of protein would provide 26.5 grams of urea nitrogen per day, and it is very likely that this would be augmented to the extent that he may have been in negative nitrogen balance. This urea nitrogen and the daily average of 8.1 grams of salt provided a minimal solute load for excre-

tion of more than 1200 milliosmoles per day. The average daily fluid intake minus a conservative estimate for insensible loss of water leaves about one liter of water each day for urine. Even if the urine had been continuously maximally concentrated he could hardly have escaped the development of a deficit of water."[1] In Welt's study the urinary electrolyte excretion was also measured and it was found that the concentration of sodium and chloride in the urine was very low despite the high levels of these ions in the serum. This low excretion of salt has been interpreted as a reaction to dehydration in which a decrease in plasma volume promotes tubular reabsorption of salt. By elimination of salt from the urine a certain amount of water can be saved. The degree to which azotemia develops in this syndrome is a function of the nitrogen and water intake and the state of renal function. In those patients in whom the latter is impaired, azotemia may develop very rapidly and to a considerable degree.

It is altogether likely that this type of dehydration occurs much more frequently than is generally appreciated since the tube feedings used in most hospitals tend to be high in protein. Smith, Wollaeger and Victor[4] in a recent study on diarrhea complicating nasogastric tube feedings note that almost all authors recommend either a moderate or high protein level in tube feeding diets. At Duke Hospital, tube feeding "A" (Table I) has been most commonly ordered with the order generally written to give the patient 2,500 ml. of this diet per day. This supplies 170 gm. of protein per day. Since we have been aware of this problem, the dietetics department has notified us every time tube feeding "A," "B" or "C" is ordered. In almost all cases the physicians ordering the diet proved to be unaware of the precise composition of the diets ordered. With the aid of the dietetics department a new tube feeding diet, "D," has been devised and is now being recommended for routine use. This diet supplies 75 gm. of protein in 2,500 ml.

It should not be inferred that high solute load is the only cause of dehydration in unconscious patients. Mention has already been made of the occurrence of simple dehydration from water lack and of the unusual type of dehydration that occurs in association with diabetes insipidus, particularly when the latter condition is not recognized. In addition, there have been a number of reports in the literature of hyperosmolarity in association with brain damage which have been attributed to a disturbance in some regulatory mechanism for salt and water excretion located in the central nervous system.[5–10] In many of these reports the evidence that the brain lesion itself was responsible for the hyperosmolarity was unconvincing because the patients in question were being tube-fed. Although the composition of diets generally was not mentioned, it may be assumed that in many cases they were high protein diets. On the other hand, there are reasons to believe that a central nervous system lesion other than one involving the hypothalamicoposterior hypophyseal system may play a role in salt and water regulation and be a factor in the development of hyperosmolarity and dehydration. Welt et al. have discussed some of the experimental evidence for this. The following case in which dehydration developed in the face of a relatively large water intake and without high protein intake and in which diabetes insipidus was not present may be an example.

Case VI. W. M. (No. C-96913), a fifty-five year old man, was admitted to the Neurosurgical Service because of progressive visual loss over two years. On examination he was found to have slurred speech, bitemporal hemianopsia and irregular pupils but no evidence of papilledema. The general physical examination was otherwise normal. Laboratory studies revealed a hemoglobin of 7 gm. per cent and a normal urine with a specific gravity of 1.016. The serum NPN was normal and PSP excretion 65 per cent in two hours. A left carotid arteriogram gave evidence of a tumor mass in the region of the anterior clinoids. A right frontal craniotomy was performed with partial removal of a suprasellar meningioma. His postoperative course was stormy with marked temperature swings from 37 to 40.5°C. He remained responsive but drowsy, lethargic, disoriented and incontinent of urine and feces. On the thirteenth postoperative day a lumbar puncture revealed findings compatible with subarachnoid hemorrhage. During this period he was being fed the regular hospital diet and full liquid diet but the precise quantities of these consumed were not recorded. Nor was his fluid intake charted accurately but there were reasons to believe that these were not adequate in the face of his fever. On the sixteenth hospital day a serum sodium of 171.4 and chloride of 124 mEq./L. and an NPN of 60 mg. per cent with a urine specific gravity of 1.012 were recorded. (Table VII.) He was seen by the present observers who recommended an increase in fluid intake by

mouth and vein to at least 4,000 ml. with subsequent efforts to maintain his fluids at a level of 1,500 ml. in excess of his output. On the seventeenth day there was no notable change in his blood values but on the nineteenth they had returned to normal. On the twenty-second and twenty-fifth days, however, hypernatremia and hyperchloremia without azotemia were noted despite a high fluid intake in conjunction with the liquid diet. Two Hickey-Hare tests were performed between the sixteenth and twenty-second days. Both showed a normal antidiuretic response to an intravenous infusion of hypertonic saline, thus ruling out diabetes insipidus. This already had seemed unlikely in view of the urine specific gravity of 1.020 on the eighteenth day. On the twenty-eighth hospital day, at a time when the patient was showing some clinical improvement, he suddenly expired, presumably from a massive pulmonary embolus.

TABLE VII
CASE VI

Hospital Day	1	2	10	16	17	18	19	22	25	28
Sodium (mEq./L.)				171.4	169.3		145.6	164.9	169.3	
Chloride (mEq./L.)				124.2	126.5		100.5	119.6	116.9	
CO_2 combining power (vol. %)				60	64		58	63	63	
Potassium (mEq./L.)				3.9	3.8		4.0	3.9	4.3	
NPN (mg. %)		30	35	64	42			32	31	Expired
Urine (vol./24 hr.)							5280		3240	
Specific gravity urine	1.016		1.010	1.012		1.020	1.004			
Fluid intake (ml.)				5430	4895	6615	4140	6480	4940	
Urinary output (ml.)				2500	1300	1365	3200	5250	3350	
Temperature (°C.)	37	37	39[6]	39[3]	39[9]	394	38	38[7]	38	
Diet	←House diet→			←——Full liquid→			← + Additional fluids——→			

Comment. Although there may have been an element of simple dehydration in this patient, the recurrence of hyperosmolarity at a time when the patient was receiving comparatively large amounts of fluids without a high protein intake suggests that some central mechanism was at play. The high specific gravity of the urine and the negative Hickey-Hare tests ruled out diabetes insipidus. This case emphasizes that there are multiple causes of dehydration, not all of which can be explained as simply as those comprising the bulk of this report.

SUMMARY

Five cases of dehydration with hypernatremia, hyperchloremia and azotemia are described in patients receiving nasogastric tube feedings. In all cases the protein intake was excessive, ranging between 125 and 200 gm. daily, and the fluid intake was inadequate to allow for excretion of all the nitrogen and other solute from the diet and from tissue catabolism. The development of the chemical abnormality was generally associated with deterioration in the clinical state of the patient. One patient died before the electrolyte disturbance was corrected. In the others, electrolyte balance was restored by either increasing the water intake or decreasing the protein intake, or both. The potential frequency and significance of this syndrome is discussed in light of the widespread usage of tube feeding diets containing moderate to high levels of protein.

Acknowledgment: We are indebted to Miss Elizabeth Yearick and Miss Gloria Kicklighter of the dietetics department of Duke Hospital for their cooperation in keeping us informed of patients being tube-fed and for preparing tube feeding "D."

Addendum: A prepared tube feeding has recently been put on the market by a well known manufacturer. The directions for its use call for making it up to contain 91 gm. of protein per liter or 210 gm. of protein in 2,300 ml. of diet. No specific recommendations for additional fluid are made.

Since submitting this manuscript we have seen a patient who developed the syndrome of dehydration with azotemia (NPN 96 mg. per cent), hypernatremia (Na 176 mEq./L.) and hyperchloremia (Cl 125 mEq./L.) while receiving the above diet as recommended plus 1,000

ml. of extra water. The patient, a young female of twenty-one years with a third degree burn, had received 175 gm. of protein and total fluid intake of 3,000 ml. for twelve days. Twenty-four hours after increasing the fluid intake to 8,000 ml., serum electrolytes and NPN were normal and there was a significant improvement in the patient's general clinical condition.

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Metabolism of Copper in Wilson's Disease and in Normal Subjects*

Studies with Cu-64

C. J. EARL, M.D.,† MILDRED JEWETT MOULTON, B.S., *and* BERTRAM SELVERSTONE, M.D.

Boston, Massachusetts

THE associated hepatic cirrhosis and degeneration of basal ganglia (hepatolenticular degeneration) described by Wilson[1] is now known to be related to an abnormality of copper metabolism.[10,18] A large number of facts are known relating to the condition but any one explanation which will account for them all is still lacking. Thus it has been established that there is an excessive amount of copper in the brain and in the liver[2–4] and that large amounts are excreted in the urine.[5,18] The level of serum copper, previously reported as high,[6] has more recently been found to be lower than normal by Bearn and Kunkel.[7] These two authors reported in the same communication a marked lowering in the level of "serum oxidase." Sheinberg and Gitlin[8] have shown a low level of caeruloplasmin in the serum of these patients, a finding which is in keeping with the low serum oxidase values found earlier by Bearn and Kunkel. More recently still, Zimdahl, Hyman and Cook[9] have measured the intake and output of copper over three-day periods in three patients and in control subjects on a normal hospital diet containing 3–6.8 mg. of copper. They report a surprisingly large positive copper balance in their patients (0.6–1.8 mg. in a three-day period) while the amounts retained by their control subjects were with the exception of one observation much lower (79 to 140 μg). In one normal subject there was actually a negative balance of 236.2 μg.

It is clear, then, that the metabolism of copper in Wilson's disease is disordered. That a causal relationship may exist between this metabolic disorder and the neurologic symptoms of the disease seems highly probable in view of the effects of treatment of the condition with dimercaprol (BAL®). The work of Denny-Brown and Porter[10,19] in particular makes it clear that great improvement may ensue if such treatment is vigorously pursued and if the patients are observed over a long enough period. The administration of BAL causes a great increase in urinary Cu excretion (up to seven times the amount excreted before treatment[10] and it is not unreasonable to attribute the subsequent improvement of these patients to diminution in the copper content of the nervous system, especially in the basal ganglia.

The present investigation sought to define further the underlying abnormality in copper metabolism. The following experiments were carried out on control subjects and in patients with Wilson's disease: (1) The levels of labelled copper in the plasma and urine after oral ingestion and after intravenous administration of Cu-64 were measured. (2) The binding of Cu-64 by the plasma proteins *in vivo* and *in vitro* has been studied.

METHODS

Preparation of Material. Cu-64 was prepared by the U. S. Atomic Energy Commission from a piece of copper wire (99.993 per cent pure) provided through the courtesy of the National Research Corporation. On arrival at the laboratory its radioactivity was about 2 mc. per mg. The wire was dissolved by heating in a small amount of concentrated nitric and hydrochloric acids, and evaporated almost to dryness. The crystals were redissolved in distilled water and gentle heating resumed until they were once

* From the Department of Neurology, Harvard Medical School, the Neurological Unit of Boston City Hospital, the Department of Neurology, Neurosurgery and Psychiatry of the New England Center Hospital, and the Department of Surgery, Tufts College Medical School, Boston, Mass.

† Eli Lilly Travelling Fellow in Medicine, Neurological Unit, Boston City Hospital.

more almost dry. Finally the crystals of cupric chloride were dissolved in distilled water to a total volume of 50 ml. An aliquot of this solution was assayed for radioactivity by means of an end-window Geiger-Müller counter.

Methods of Assay. Assays of radioactivity of plasma and urine after oral administration of Cu-64 were made with a dipping Geiger-Müller counter.[11] After intravenous administration of Cu-64, 0.1 ml. of plasma was placed on lens tissue in a planchet and radioactivity assayed with an end-window Geiger-Müller counter. With the dip counter persistent contamination of the glass envelope was at first a problem. This was effectively eliminated by washing the counter and cell with a solution of calcium disodium versenate (ethylene-diamine-tetra-acetate). Our dip counting technic provided a direct estimation of the *concentration* of labelled copper in the plasma. Results by these two methods proved to be related in a linear fashion but data were not intermixed in a single experiment.

For the estimation of radioactivity in samples used for some of the experiments on plasma proteins fractions, a sulfide precipitation technic was employed which made concentration of the labelled copper possible.[12] One or 2 ml. of plasma were ashed with sulfuric acid and hydrogen peroxide (superoxol) and the following were added: (1) 1 ml. of copper sulfate solution containing 10 mg. of copper/ml.; (2) 7 ml. of concentrated ammonium hydroxide, sp. gr. 0.880; (3) 1 ml. of sodium sulfide solution containing 60 mg. of sulfide/ml. The precipitate of insoluble copper sulfide was filtered in a Gooch crucible on filter paper just large enough to fit an aluminum planchet, and assayed for radioactivity by means of an end-window Geiger-Müller counter. The method was found to give counting rates which were consistently proportional to measured quantities of a standard solution of Cu-64.

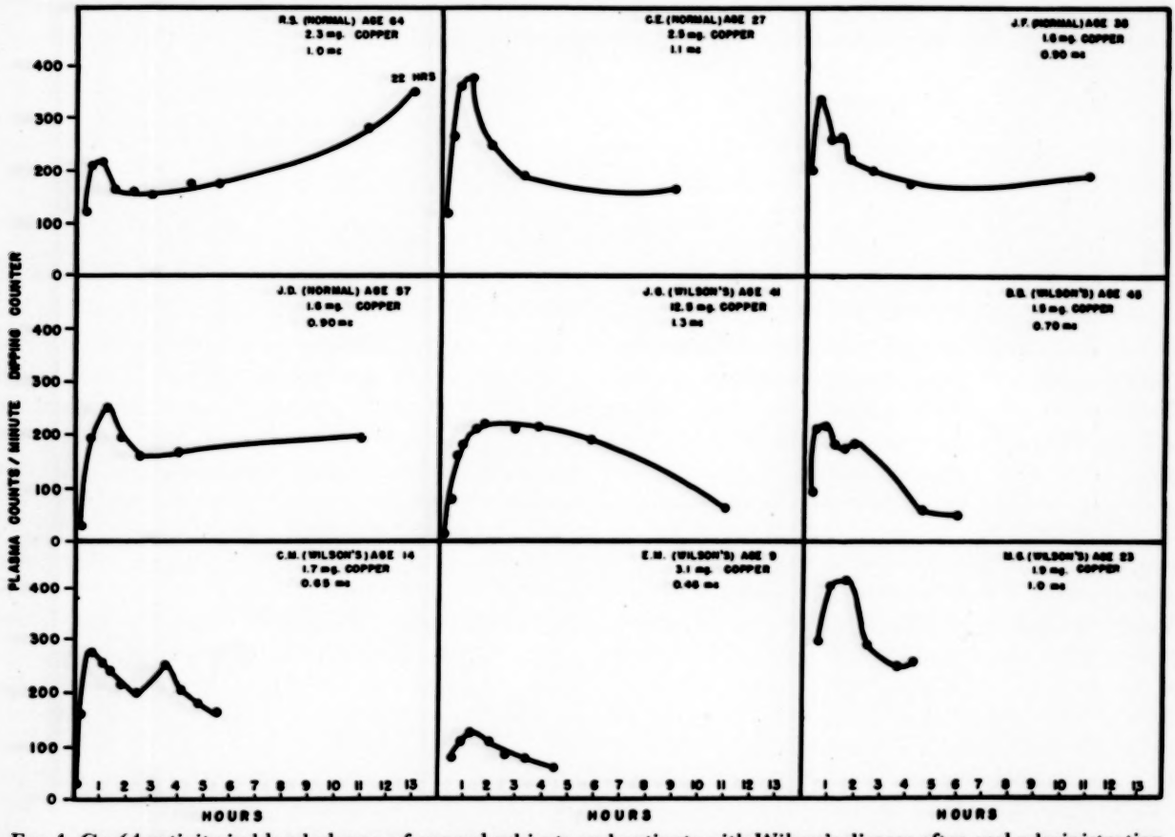

FIG. 1. Cu-64 activity in blood plasma of normal subjects and patients with Wilson's disease after oral administration of Cu-64 Cl_2. (Note that last point for subject R. S. was at twenty-two hours.)

Estimations of Cu-64 in Plasma and Urine: Oral administration: Adult subjects were given about 1 mc. of labelled cupric chloride in approximately 250 ml. of water. Younger patients received proportionately smaller doses. The activity and the total amount of copper including carrier administered are shown for each case in

Figure 1. The total amount of Cu administered varied from 1.5 to 12.5 mg. Venous blood was drawn at the times shown. In the earliest experiments the last sample was taken about six hours after administration of Cu-64. In view of subsequent findings (*vide infra*) samples were taken after twenty-four hours in later cases. The blood samples were placed in tubes containing dried heparin, the plasma was separated by centrifugation and radioactivity assayed with a dip counter. The bladder was emptied at the beginning of the experiment and subsequently, whenever possible, at the end of each experimental hour. The volume of urine passed was measured and radioactivity assayed with the dip counter.

Intravenous administration: A solution of Cu-64 was prepared to contain at the time of injection about 0.05 mc./ml. with a total copper concentration of about 50 μg./ml. A dose of 2 ml. was given into the antecubital vein of one arm. Samples of venous blood were drawn from the other arm at the times shown in Figure 2 during the next hour. At the end of the hour the bladder was emptied. Another sample of blood was drawn twenty-four hours later. The radioactivities of the plasma and urine were estimated with the end-window Geiger-Müller counter.

The Binding of Cu-64 by Plasma Protein Fractions: Plasma taken after Cu-64 administration and plasma mixed *in vitro* with solutions containing $Cu\text{-}64^{++}$ were used. Three forms of experiment were done: (1) ultrafiltration, (2) precipitation of all proteins, (3) fractional precipitation of proteins.

Ultrafiltration: The ultrafiltration method was a simple one and was suggested to us by Dr. Edward Frieden of the New England Center Hospital. About 2 ml. of plasma containing Cu-64 were pipetted into narrow bore (0.5 cm.) cellophane dialysis tubing about 15 cm. long. The ends of the tubing were brought together. The loop thus formed with the plasma in the dependent part was then placed in a 15 ml. conical centrifuge tube. The free ends of the tubing were folded over the top edge and secured with adhesive cellophane tape. The tube was covered with a rubber cap and centrifuged for two hours at approximately 2,500 RPM in a bench centrifuge. During this time just over 0.2 ml. of protein-free filtrate was obtained by this method. The dialysis tubing was carefully removed and 0.1 ml. of the ultrafiltrate was placed on a planchet for assay; 0.1 ml. of the unfiltered plasma was similarly assayed.

Total precipitation of proteins was carried out by 70 per cent saturation of plasma with ammonium sulphate.

Fractionation: Precipitation of the "globulin" fraction of the plasma proteins was carried out by 50 per cent saturation with ammonium sulfate. One volume of a saturated solution of ammonium sulfate was added to one volume of plasma, mixed well, and allowed to stand with occasional agitation for twenty minutes. An aliquot of this mixture was taken for assay of radioactivity and the remainder filtered. An equal aliquot of the filtrate was taken for assay by the same method used for assay of the mixture.

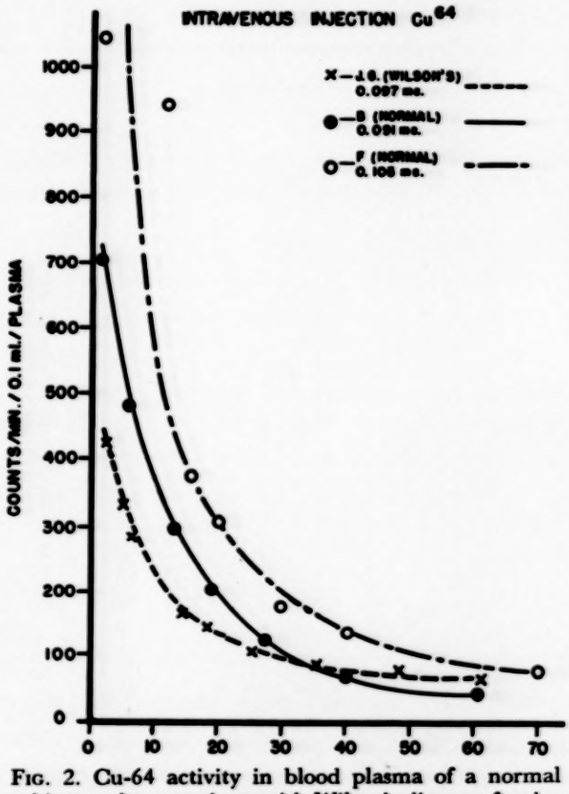

FIG. 2. Cu-64 activity in blood plasma of a normal subject and two patients with Wilson's disease after intravenous injection of Cu-64 Cl_2.

These fractionations are of the simplest sort and a detailed protein fractionation would be very valuable. This is made difficult by the small amounts of Cu-64 present in the blood *in vivo* and by the short half-life of the isotope. Unsuccessful attempts were made to get more information by sodium sulfate fractionation and by electrophoresis on filter paper.

RESULTS

Estimations of Total Plasma and Urine Cu-64. Oral administration: The findings by oral admin-

istration are illustrated in Figure 1 and Table 1. In the four normal subjects radioactivity was always detected in the first blood sample usually drawn less than fifteen minutes after the dose. There was a rapid rise to a maximum value at about one hour after administration. The radioactivity then fell quite sharply for about three hours, following which the fall became much more gradual. In three of the four subjects the radioactivity rose in later samples. In one of these a sample taken twenty-two hours after administration of Cu-64 showed an activity as high as any of the earlier samples.

In the five patients with Wilson's disease the blood levels of Cu-64 rose at about the same rate as in the normal controls. In four of the patients there was a fairly rapid initial fall similar to that in the normal subjects. In the two cases in which samples were taken at later intervals, however, no tendency to rise above earlier levels was noted. In patient J. G. the initial rate of fall was extremely slow. As can be seen in Figure 1, levels of radioactivity in his plasma fell hardly at all for six hours. It is interesting that this patient had the more slowly progressive "pseudosclerotic" type of Wilson's disease as contrasted with the other four patients who had the more rapidly advancing "progressive lenticular degeneration."

Cu-64 appeared rapidly and in high concentration in the urine of the patients with Wilson's disease. The hourly excretion of the isotope in the urine of control subjects was much lower, as shown in Table 1; the difference in urinary Cu-64 *concentration* between the two groups was even more striking. In one patient with Wilson's disease (J. G.) an astounding amount of Cu-64 was excreted in each of the five periods studied. This patient was, interestingly enough, the one with a pseudosclerotic form of the disease whose plasma level of Cu-64 remained high for six hours.

TABLE 1
URINARY EXCRETION OF CU-64

Wilson's Disease						*Normal Subjects*					
Patient	Hours	c/m Conc.	Vol.	Vol. × Conc.	"Clearance"	Patient	Hours	c/m Conc.	Vol.	Vol. × Conc.	"Clearance"
J. G.	1	348	120	41,800	.....	C. E.	1	24.4	94	2,290	.....
	2	265	84	22,200	1.7		2	31.7	76	2,408	0.1
	3	304	262	79,600	6.1		3	10.5	275	2,880	0.22
	4	163	258	42,100	3.24	J. D.	1	13.9	65	905	.....
	5	348	232	80,700	6.56		2	55.6	13.5	750	0.069
D. B.	1	52.8	100	5,280	.....		3	8.6	125	1,075	0.065
	2	14.1	175	2,450	0.234		4	7.6	100	760	0.070
	3, 4	49.1	130	6,380	0.41	R. S.	1	14.4	135	1,945	.....
	5	126	60	7,560	2.13		2, 3	22.8	145	3,310	0.147
E. M.	1	42.2	lost	.....	.....		4	15.2	265	4,030	0.414
	2	184	42.5	7,830	1.12	J. F.	1	0.9	380	342	.....
	3	105.2	39.0	4,100	0.68		2	21.0	85	1,780	0.118
	4	126.4	25.4	3,200	0.53		3	12.5	275	3,440	0.28
							4	12.6	195	2,460	0.22

It will be seen, too, in Table 1 that the total amount of isotope copper excreted in the urine varied from hour to hour. This variation did not bear any constant relation to the mean level of Cu-64 in the plasma during the hour in which the urine was passed. This observation we are unable to explain; it is interesting that one of us (C. E.) has found that excretion of total copper in patients with Wilson's disease may also vary markedly from hour to hour. In patient J. G., for example, total copper excretion measured over two-hour periods varied, on nineteen separate occasions, from 44 to 157 μg.

Figures for urinary "clearance" of Cu-64 from plasma have been calculated by dividing the total activity of Cu-64 excreted by the mean plasma concentration during the appropriate interval. These data are shown in Figure 3. There appears to be, with the exception of a single

point, no overlap between the normal controls and patients with Wilson's disease.

After intravenous injection (Fig. 2) the concentration of Cu-64 in the plasma falls rapidly and can be expressed as the sum of two exponential functions. The first function had a half-time of 6.5 minutes in each of two normal subjects and of 4.7 minutes in one patient with Wilson's disease. The second member had a half-time of 30 minutes and of 34 minutes in the normal subjects, as contrasted with 58 min. in the patient with Wilson's disease. Additional patients must be studied before any significance can be attached to this disparity.

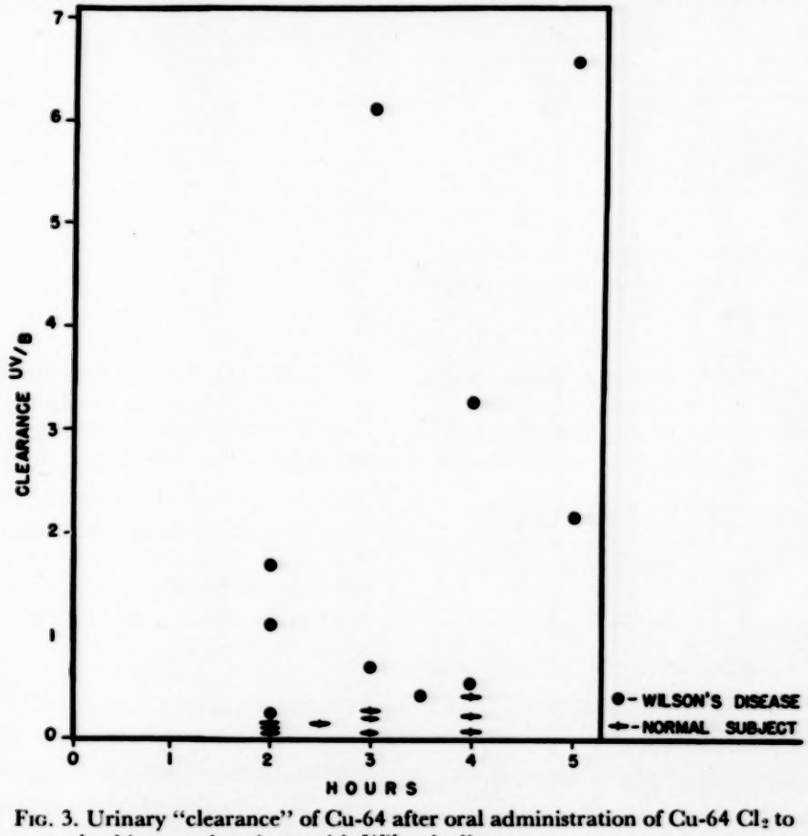

FIG. 3. Urinary "clearance" of Cu-64 after oral administration of Cu-64 Cl_2 to normal subjects and patients with Wilson's disease.

Binding of Cu-64 by Plasma Protein Fratcions. Since a marked deficiency of caeruloplasmin has been demonstrated in Wilson's disease,[8] it was thought important to investigate the distribution of labelled copper among the plasma proteins.

In vitro studies: When radioactive cupric chloride was added to plasma from normal subjects and from patients with Wilson's disease, only about 0.2 to 0.4 per cent of the activity passed through a cellophane membrane. Previous studies with non-radioactive copper[13] have failed to demonstrate the passage of ions through such a membrane. The small but detectable amount of $Cu\text{-}64^{++}$ clearly present in the ultrafiltrate is an indication of the sensitivity of the isotope technic and not of a difference between the chemical properties of stable and of radioactive copper. The following data are illustrative:

	Counts/min./0.1 ml.	
	Plasma	Ultrafiltrate
Normal subjects:		
1	6,383	17.8
2	6,345	18.6
Wilson's disease:		
1	6,530	14.3
2	2,454	10.0

When Cu-64 was added to plasma and the protein precipitated by 70 per cent saturation with ammonium sulfate, most of the radioactivity remained in the precipitate. This was true

whether normal plasma or plasma from patients with Wilson's disease was studied. The results are as follows:

	Total Counts/0.1 ml./ min.	Filtrate Counts/0.1 ml./ min.
Normal plasma....	293	13.9
Plasma from Wilson's disease..	298	6.85

On the other hand, when precipitation was carried out at 50 per cent saturation, almost all the radioactivity appeared in the filtrate. When plasma to which Cu-64 had been added was allowed to stand for twenty-four hours, little change occurred in the small amount of Cu-64 precipitated when the ammonium sulfate was added.

	Counts/min./0.1 ml.		
	Total	Filtrate	Filtrate/ Plasma
Normal plasma			
0 hr	2,440	2,300	0.94
15 hr	2,650	2,645	0.99
23 hr	2,680	2,670	0.99
42 hr	2,520	2,550	1.02
Plasma from patient J. G.			
0 hr	3,500	3,330	0.93
23 hr	4,060	3,560	0.88
42 hr	3,810	3,440	0.90

In vivo studies: When Cu-64 was administered *in vivo*, results with 70 per cent saturation with ammonium sulfate were quite in keeping with the *in vitro* studies.

After *in vivo* administration of Cu-64 a strikingly different precipitation pattern was found in patients with Wilson's disease as compared with normal subjects, when plasma protein was fractionated by half saturation with ammonium sulfate. This is well shown in the following figures comparing the activity precipitated from samples taken during the first hour after administration with the activity precipitated in samples taken after twenty-four hours (see also Fig. 4):

	Time	Total	Filtrate	F/T
Normal subjects				
A. M.	1 hr.	90.6	70.4	0.78
	24 hr.	123.9	27.6	0.22
R. S.	0.6 hr.	42.3	34.2	0.81
	22 hr.	37.7	5.2	0.14
J. F.	1 hr.	594	439	0.74
	26 hr.	153	56	0.37
Wilson's disease				
J. G.	1 hr.	1,980	1,351	0.68
	24 hr.	171	127.5	0.75
M. G.	1 hr.	1,817	1,752	0.96
	24 hr.	308.9	316.9	1.025

COMMENTS

The known facts about copper metabolism in Wilson's disease, as outlined in the introduction, raise puzzling questions concerning its pathogenesis. On the one hand there is an excessive urinary excretion of copper and a low level of copper and caeruloplasmin in the plasma, while on the other hand there is an excessive amount of copper in the brain and liver. One explanation which may be offered to cover the known facts would suppose that the basic defect is a failure of synthesis of caeruloplasmin at a normal rate. As a result there is present in these patients an amount of "unattached" copper free to combine in other ways. This "unattached" copper, it is supposed, is available for binding, for example, to the proteins of the liver and brain. It is also excreted by the kidney. Bearn[14] suggests that the low caeruloplasmin levels might lead to increased absorption of dietary copper. This attractive but unproved hypothesis would explain also the increase in excretion of copper in the urine which follows ingestion of amino acids in these patients but not in normal subjects.[13] The copper of caeruloplasmin and perhaps also of other unknown complexes in the tissues of normal persons is bound firmly and, as we have shown, the copper of caeruloplasmin will not exchange with labelled copper added to the plasma *in vitro*. According to our hypothesis, in Wilson's disease the excess copper in the tissues is *not* firmly bound and can therefore more readily form complexes with amino acids than the copper which is firmly bound in normal tissues. The increased formation of these soluble and diffusible amino acid complexes of copper could explain the large amounts of copper excreted in

the urine of these patients after ingestion of amino acids.

Failure of synthesis of caeruloplasmin in patients with Wilson's disease is further suggested by our results with fractionation of plasma proteins by half saturation with ammonium sulfate. In normal subjects given oral or intravenous doses of Cu-64 ions, early plasma samples showed that most of the labelled copper remained in the "albumin" fraction. Samples taken after twenty-four hours showed that the labelled copper had transferred, for the most part, to the "globulin" fraction with which caeruloplasmin is ordinarily precipitated. In the two patients with Wilson's disease in whom these studies were undertaken the labelled copper remained in the "albumin" fraction, for the most part, even after twenty-four hours. These data, then, provide further evidence for the hypothesis that caeruloplasmin, the copper-containing protein known to be deficient in Wilson's disease,[7,8] is not synthesized at a normal rate in these patients. We were not able to establish that the normal "globulin Cu-64 complex" was caeruloplasmin although we attempted by electrophoresis on filter paper[16] to define more accurately by radioautography the globulin fraction which was concerned. Our attempts were unsuccessful because, after a safe dose of the rapidly decaying Cu-64, the initial plasma activity was low and because the amount of plasma which could be applied to the paper strip was small. Bearn and Kunkel (personal communication) have been able to demonstrate by starch-zone electrophoresis that the globulin fraction with which the Cu-64 is associated after twenty-four hours in normal patients is, in fact, caeruloplasmin. That copper *recently* absorbed from the alimentary canal is certainly not for the most part bound in caeruloplasmin is shown by the fact that from 74 to 96 per cent of the total plasma Cu-64 remains with the "albumin" fraction. Were it present as caeruloplasmin it would be precipitated with the "globulin" fraction.[17] The physiologic role of caeruloplasmin is at present unknown, but it would seem certain from our findings that it is not engaged, at least in the early stages after absorption, in the transport of copper in the body. Whether caeruloplasmin copper is subsequently available to tissues we cannot say, but in view of the difficulty of dissociation of the complex this seems unlikely. The recently absorbed copper not precipitated with the "globulin" fraction may be bound either by albumin or perhaps with the metal-combining globulin fraction described by Surgenor, Koechlin and Strong.[15] This latter, the normal iron-binding protein in serum, is described as a globulin but, like albumin, is not precipitated at 50 per cent saturation with ammonium sulfate.[17]

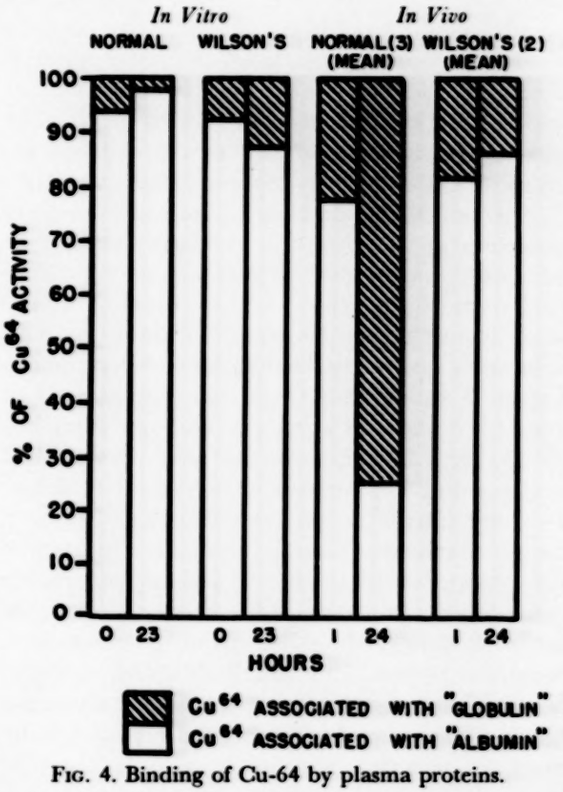

FIG. 4. Binding of Cu-64 by plasma proteins.

Unexpectedly perhaps, the uptake curves in the plasma after oral administration of Cu-64 showed no striking differences in the two groups except in the case of J. G. in whose plasma high levels persisted for six hours. In three normal subjects the fall in the plasma level which ordinarily occurs after about one hour was followed several hours later by a tendency of the Cu-64 activity of the plasma to rise. In one case, R. S., this was particularly striking and the level at twenty-four hours was higher than at any previous time. Similar high figures were reported by Schubert and Riezler.[12] These later blood samples were not taken in the earliest subjects studied, among whom were four of our five patients who unfortunately were not again available for investigation. The significance of this delayed rise is not clear. We thought at first that later absorption of the isotope from the alimentary canal might explain it. This seems unlikely since consideration of the results in the case of R. S.

shows that at a time when the serum Cu-64 level was showing its late rise (twenty-two hours after administration) the labelled copper of the plasma was bound chiefly to the globulin fraction of the plasma proteins. Since this transfer of the Cu-64 to the globulin fraction requires many hours, we can assume that the late rise in plasma activity could have been produced by recently absorbed copper. It is possible that copper is abstracted, perhaps by the liver, from the plasma and is later released as caeruloplasmin. Such a mechanism could give rise to the delayed increase of Cu-64 activity of the plasma.

The variation from hour to hour in the rate of excretion of the Cu-64 in the urine cannot be adequately accounted for but may be related to variations in the rate of absorption of amino acids from the alimentary canal since the subjects were not in the fasting state. Nevertheless, Figure 3 shows that when the "clearance" of Cu-64 is compared from hour to hour, there is a rather clear demarcation between the control subjects and the patients with Wilson's disease. In our ultrafiltration experiments we have demonstrated that a small but definite fraction of the copper added *in vitro* to plasma will pass a cellophane membrane. This is true whether or not the plasma is taken from patients with Wilson's disease. This small diffusible fraction could permit copper simply to pass the glomerular membrane of the kidney and eliminates the need to consider a tubular or other specific lesion. Further, as Matthews et al. have pointed out,[13] the concentrating power of the kidney is such that only a very small increase in this diffusible fraction would be necessary for the passage of the large amounts of copper excreted by these patients.

SUMMARY

1. A solution of labelled cupric chloride ($Cu\text{-}64Cl_2$) has been administered orally to five patients with Wilson's disease and to four normal subjects, and the Cu-64 activity of the plasma and urine has been studied. A similar investigation has been carried out after intravenous administration of $Cu\text{-}64Cl_2$ to two normal subjects and to one patient with Wilson's disease.

2. Curves of plasma Cu-64 activity were surprisingly similar in the two groups. Urinary "clearance" of Cu-64 was, however, much greater in patients with Wilson's disease than in normal subjects.

3. Simple fractionation of the plasma proteins provides additional evidence that the specific defect in Wilson's disease is a failure of synthesis of caeruloplasmin. A hypothesis is presented by which the associated biochemical abnormalities of the disease may be explained on this basis.

4. *In vitro*, a small amount of diffusible labelled copper can be demonstrated by ultrafiltration of serum to which $Cu\text{-}64Cl_2$ has been added.

Acknowledgments: We are indebted to Dr. D. Denny-Brown for access to his patients at the Neurological Unit, Boston City Hospital, Boston, Mass. The U. S. Atomic Energy Commission provided the radioactive material used in these studies.

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N-allylnormorphine (Nalline) Action on Narcotized and Non-narcotized Subjects*

A. SALOMON, M.D., P. S. MARCUS, M.D., J. A. HERSCHFUS, M.D. *and* M. S. SEGAL, M.D.
Boston, Massachusetts

RESPIRATORY depression following the use of narcotics is commonly observed and is a most dangerous symptom of opiate intoxication. Treatment in the past has been largely symptomatic and supportive, and in many instances has been unsuccessful. Consequently the introduction of N-allylnormorphine (nalline® †) into the therapy of opiate intoxication is of great significance. Nalline effectively counteracts the respiratory depression of narcotic overdosage and, in contrast to other analeptics, has a specific action.

Chemically, nalline differs from morphine in that the methyl group is replaced by an allyl group. Simple demethylation of morphine, codeine and other related alkaloids diminishes their analgesic potency.[1] Substitution of an allyl for the methyl group qualitatively alters the pharmacologic action of the drug.[2] N-allylnorcodeine was reported by Pohl[3] to stimulate respiration and to counteract the respiratory depressant effect of morphine. McCawley et al.[4] and Hart[5] found N-allylnormorphine to be even more effective in this regard.

Further investigations on the pharmacologic action of nalline in animals were carried out by several authors.[6–8] In dogs nalline produced no respiratory depression in doses up to 10–20 mg. per kg. of body weight. Given an hour before morphine administration, nalline inhibited its respiratory depressant action; and given up to two or three hours afterward, effectively counteracted it. Given to dogs with severe morphine intoxication, normal behavior returned within fifteen minutes. Customarily fatal doses of morphine were harmless to mice that had been protected with nalline. Cats were relieved by nalline of morphine-induced respiratory depression without apparent interference with analgesia.

The effect of nalline on opiates other than morphine was studied by Huggins et al.[9] They found that intravenous nalline protected dogs against fatal respiratory depression due to methadone, metapon, dilaudid® and codeine, as well as morphine.

The action of nalline on narcotized and non-narcotized human subjects was recently described by several investigators. In non-narcotized individuals Eckenhoff et al.[10] observed that the intravenous administration of 5–10 mg. of nalline resulted in a minor drop in respiratory rate, an average decrease of 35 per cent in respiratory minute volume and little or no change in pulse or blood pressure. In all of the cases there was a definite sedative effect. The toxic action of non-narcotic agents, including barbiturates and ether, was found to be unaffected by nalline administration.

In narcotized human subjects[11,17] nalline was found to be as effective in overcoming respiratory depression as in the case of animals. Morphine and related drugs, including demerol,® were inhibited or counteracted equally well. Its effect on other than respiratory toxic manifestations, i.e., coma and circulatory disturbances, was found to be variable, and generally appeared to be less dramatic than relief from respiratory depression.

The present study was an attempt further to evaluate[15] the action of nalline on narcotized and non-narcotized subjects. Six separate groups totaling twenty-nine individuals were studied.

RESULTS

1. Thirteen cases of severe respiratory depression induced by natural or synthetic alkaloids were treated with nalline. (Table 1.) Six of these

† Kindly supplied by Merck & Co., Inc., Rahway, New Jersey.

* From the Department of Medicine, Tufts College Medical School, and the Departments of Inhalational Therapy and Anesthesiology, Boston City Hospital, Boston, Mass. This paper was presented in part at the Boston Chapter, American Federation for Clinical Research, December 3, 1953.

TABLE 1

RESPIRATORY DEPRESSION DUE TO OPIATE INTOXICATION

Observations in Thirteen Patients before and after the Administration of Intravenous Nalline

History	Opiate and Nalline Administration and Time of Observation (min.)	Respiratory Rate	Depth of Respiration	Pulse	Blood Pressure	Deep Tendon Reflexes*	Consciousness*
1. P. C.; female; 69 yr. hypertension, coronary disease, congestive failure; given medication over 7 hr. period because of severe pain resembling coronary attack	Demerol, 100 mg. p.o.	.....	.....	.....	.....	.....	.....
	Morphine, ¼ gr. p.o.	.....	.....	.....	.....	.....	.....
	Morphine, ¼ gr. s.c.	8	1+	100	200/110	0	0
	Nalline, 5 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 10 mg. in 200 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	24	4+	90	200/110	0	±
	15	19	4+	90	200/110	0	2+
	30	20	4+	90	200/110	0	2+
	45	20	4+	90	200/110	0	2+
	60	20	4+	90	200/110	1+	3+
2. M. H.; female; 61 yr. Received morphine for dyspnea; respiratory rate, 30; wheeze, 4+, incipient pulmonary edema(?)	Morphine, ⅙ gr. s.c.	8	4+	78	160/70	1+	±
	Nalline, 10 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 10 mg. in 400 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	20	4+	78	160/80	2+	±
	15	16	4+	78	160/80	2+	1+
	30	16	4+	78	160/80	2+	3+
	45	18	4+	78	160/80	2+	3+
	60	20	4+	78	160/80	3+	3+
3. A. C.; female, 82 yr. Incipient pulmonary edema; left heart failure	Morphine, ¼ gr. s.c.	5	1+	110	210/110	2+	±
	Nalline, 5 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 10 mg. in 300 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	12	4+	90	190/90	2+	1+
	15	12	4+	90	190/90	2+	Irrational, excited
	30	9	4+	100	190/90	2+	Irrational, excited
	Nalline, 5 mg. i.v.	.....	.....	.....	.....	.....	.....
	Immediate	14	4+	100	190/90	2+	Irrational, excited
	45	14	4+	100	190/90	2+	2+
	60	18	4+	100	190/90	2+	3+
4. L. V.; Male; 83 yr. Chronic bronchitis, bronchiectasis, hemoptysis in the past, pulmonary emphysema, prostatic enlargement, bronchopneumonia	On admission	26	4+	88	130/50	2+	4+
	Demerol, 100 mg. 2 × total 200 mg. s.c.	3	4+	60	100/60	1+	±
	Nalline, 5 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 5 mg. in 300 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	20	4+	86	130/50	2+	+
	15	13	4+	100	130/50	2+	3+

TABLE 1 (*Continued*)

History	Opiate and Nalline Administration and Time of Observation (min.)	Respiratory Rate	Depth of Respiration	Pulse	Blood Pressure	Deep Tendon Reflexes *	Consciousness *
	Nalline, 5 mg. i.v.	.....	.....	.....	.....	.....	.....
	Immediate	16	4+	88	130/50	2+	3+
	30	18	4+	100	130/50	2+	3+
	45	18	4+	100	130/50	2+	3+
	60	20	4+	100	130/50	2+	4+
5. C. M.; male; 79 yr. Substernal pain associated with angina pectoris	Morphine, ½ gr. s.c.	18	.....	.....	.....	.....	.....
	Demerol, 75 mg. s.c.	7	2+	108	120/80	2+	1+
	Nalline, 10 mg. i.v.	.....	.....	.....	.....	.....	.....
	Immediate	17	3+	108	135/80	4+	3+
	15	26	3+	108	140/80	4+	4+
	30	17	3+	108	140/80	4+	4+
	Nalline, 30 mg. in 200 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	45	24	2+	108	144/100	4+	3+
	60	22	2+	108	140/96	4+	4+
6. L. D.; female; 78 yr. Incarcerated inguinal hernia	Morphine, ½ gr. s.c.	3	4+	88	90/70	1+	0
	Nalline, 5 mg. i.v.	.....	.....	.....	.....	.....	.....
	Immediate	3	4+	88	90/70	1+	0
	15	12	4+	80	120/80	1+	2+
	30	10	3+	84	120/80	3+	2+
	Nalline, 10 mg. in 200 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	14	4+	80	170/85	3+	3+
	45	13	4+	80	170/85	3+	3+
	60	14	4+	80	170/85	3+	3+
7. W. McM.; male; 64 yr. Cleaning of burn on right foot due to spilled molten solder	Pentothal, 200 mg. i.v.	20	4+	90	160/80	2+	0
	Demerol, 50 mg. s.c.	.....	.....	.....	.....	.....	.....
	Nisentil, 60 mg. i.v.	2	4+	75	120/40	1+	0
	Nalline, 10 mg. i.v. followed by Nalline, 20 mg. in 1000 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	16	4+	75	120/40	2+	1+
	15	16	4+	75	130/80	2+	1+
	30	18	4+	85	160/80	3+	2+
	45	18	4+	90	160/80	3+	2+
	60	18	4+	90	160/80	3+	2+
8. Male; 12 yr. † Spinal fusion severe scoliosis due to poliomyelitis, chest expansion very poor due to paralysis of musculature	Codeine, 60 mg. 2x total 120 mg. s.c.	14	1+	50	50/0	1+	0
	Nalline, 5 mg. i.v.	.....	.....	.....	.....	.....	.....
	Immediate	20	4+	70	70/0	2+	1+
	15	20	4+	70	100/60	2+	3+
	30	20	4+	70	100/60	2+	3+
	45	20	4+	70	100/60	2+	3+
	60	20	4+	70	100/60	2+	3+

TABLE 1 (*Continued*)

History	Opiate and Nalline Administration and Time of Observation (min.)	Respiratory Rate	Depth of Respiration	Pulse	Blood Pressure	Deep Tendon Reflexes*	Consciousness*
9. J. H.; Male; 80 yr. Hernioplasty	Demerol, 50 mg. s.c.	20–10	3+	80–60	128/84–54/40	3+–1+	2+
	Nalline, 10 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 10 mg. in 500 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	22	2+	64	78/60	2+	3+
	15	18	3+	72	108/60	2+	4+
	30	20	3+	68	120/70	2+	4+
	45	18	3+	80	120/70	2+	4+
	60	20	3+	80	120/70	2+	4+
10. S. Mc M.; female; 80 yr. Excision of carotid tumor, benign	Pentothal, 1 gm. i.v.	18	3+‡	80	150/80	2+	0
	Morphine, 1/6 gr. s.c.	6	C.S.	56	210/90	1+	0
	Nalline, 10 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 10 mg. in 500 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	14	4+	64	195/90	2+	1+
	15	12	4+	70	158/60	2+	3+
	30	14	4+	68	150/60	2+	Irrational, excited
	45	14	4+	68	150/60	2+	3+ Irrational, excited
	60	14	4+	68	150/60	2+	2+
11. A. G.; male; 65 yr. Retrograde prostatectomy	Morphine, 1/6 gr. s.c.	20–1	3+‡ C.S.	100–145	230/100	2+	0
	Nalline, 5 mg. i.v.	.....	.....	.....	.....	.....	.....
	Immediate	Irregular	3+	140	140/100	2+	0
	15	Irregular	3+	100	180/100	2+	0
	Nalline, 5 mg. in 500 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	25	4+§	120	210/100	2+	1+
	30	20	4+	120	210/100	2+	1+
	45	20	4+	120	210/100	2+	1+
	60	20	4+	120	210/100	2+	1+
12. M. M.; female; 84 yr. Perforated gall bladder	Morphine, 1/6 gr. 3x total 1/2 gr. s.c.	24–Apnea	4+– Artificial respiration	80–40	110/90–70/40	2+–0	3+–0
	Nalline, 10 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 5 mg. in 300 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	24	4+	80	110/60	1+	0
	15	20	4+	80	110/60	2+	0
	30	20	4+	80	110/60	2+	0
	45	20	4+	80	110/60	2+	0
	60	20	4+	80	110/60	2+	3+

TABLE I (*Continued*)

History	Opiate and Nalline Administration and Time of Observation (min.)	Respiratory Rate	Depth of Respiration	Pulse	Blood Pressure	Deep Tendon Reflexes *	Consciousness *
13. E. H.; female; 36 yr. Surgery for carcinoma thyroid	Morphine, 1/6 gr. s.c.	18–4	4+	70–100	140/80–110/70	2+–1+	0
	Nalline, 5 mg. i.v. followed by	.....	.....	.....	.....	.....	.....
	Nalline, 5 mg. in 500 cc. 5% G/W i.v.	.....	.....	.....	.....	.....	.....
	Immediate	18	4+	70	110/70	2+	0
	15	16	4+	60	140/80	2+	0
	30	18	4+	60	140/80	2+	0
	45	18	4+	60	140/80	2+	0
	60	18	4+	60	140/80	2+	1+

* Depth of respiration, tendon reflexes and degree of consciousness are graded from 4+ to 0, 4+ indicating normal status and 0 indicating marked decrease.

† Presented through the courtesy of Drs. E. Black and Roberts of the North Carolina Orthopedic Hospital.

‡ Cheyne-Stokes

§ Even

had received, in addition to opiates, a variety of non-narcotic agents for the purpose of anesthesia. Severe respiratory depression was the most prominent toxic manifestation in all, the rate of breathing ranging from ten per minute to complete apnea. In addition to being slow, respiration was shallow and ineffectual in several, and two patients exhibited Cheyne-Stokes breathing. Cyanosis of some degree was invariably present. The circulatory system was more often affected in the older patients; in several, blood pressure dropped to shock levels, while in others an elevation was observed. Deep tendon reflexes were usually depressed; but when respiratory depression was of short duration, they were unaffected. Myosis was present in all instances. The level of consciousness was also affected but this was difficult to evaluate because of the administration of other medications or because of the critical condition of the patient.

Following the intravenous administration of 5 to 10 mg. of nalline there was rapid improvement in all patients. The most striking effect was on the respiratory rate, which began to rise in fifteen to thirty seconds and reached a minimum of fourteen respirations per minute in all cases. Concomitantly the respirations deepened and cyanosis disappeared. In several cases the respiratory rate began to decline again, requiring a second dose of nalline. Consequently we established the routine of following our initial intravenous dose with an additional 5 to 10 mg. in 200 to 500 cc. of glucose in water, given by slow intravenous infusion. This prevented any subsequent decline in respiration.

The beneficial effects of nalline on the circulation were more gradual. The blood pressure gradually returned from depressed or elevated levels produced by opiates or hypoventilation to the usual level for that patient. When the blood pressure remained within the normal range, no significant changes occurred. Soon after nalline administration most of the patients became more responsive and could be aroused. However, the awakening effect was incomplete, and if the patients were not disturbed, they would fall asleep again. Myosis persisted much longer than the other effects of opiate intoxication.

Arterial blood studies were made in two patients with severe respiratory depression before and at intervals after the intravenous administration of nalline. The data in Table II show that after nalline was given there was a prompt fall in the abnormally high CO_2 tension, with a concomitant rise in blood pH and blood buffer base toward normal levels.

II. Two patients were given intravenous demerol during surgical procedures (resection of mandible and hip nailing). Postoperatively no respiratory depression was noted but the patients

failed to awaken within the expected period. Each was given 10 mg. of nalline intravenously, and each immediately became alert and responsive. Neither exhibited any subsequent respiratory depression which might be attributed to nalline.

III. Two patients with chronic pulmonary emphysema and chronic hypoxia were given ⅜ and ½ gr. of morphine sulfate, respectively, to produce respiratory depression. When the respiratory rate dropped well below normal levels, 10 mg. nalline was given intravenously, followed by 10 mg. in 5 per cent glucose in water, in a slow drip infusion. Control studies,

TABLE II

ARTERIAL BLOOD STUDIES IN TWO PATIENTS WITH RESPIRATORY DEPRESSION DUE TO OPIATE INTOXICATION

Observations before and Fifteen and Sixty Minutes after Administration of Intravenous Nalline

Patient	Time of Determination (min.)	CO_2 Tension (mm. Hg)	CO_2 Content (vol. %)	Buffer Base (mEq./L.)	O_2 Content (vol. %)	O_2 Capacity (vol. %)	O_2 Saturation (%)	pH
1. L. D.	Control	94	56.93	41	19.74	20.46	96.48	7.08
	15	50	41.52	42	20.32	20.46	99.32	7.23
	60	40	48.45	51	18.79	20.22	92.92	7.41
2. C. M.	Control	52	47.49	48	18.02	19.49	92.46	7.32
	15	42	47.66	52	18.30	19.49	93.89	7.42
	60	44	42.01	49	18.13	19.49	93.02	7.35

TABLE III

CIRCULATORY AND VENTILATORY CHANGES

Studies in Two Patients with Severe Chronic Pulmonary Emphysema after Administration of Morphine Followed by Intravenous Nalline

Patient	Administration of Morphine and Nalline and Time of Observation (min.)	Respiratory Rate	Depth of Respiration*	Pulse	Blood Pressure	Pupils*	Deep Tendon Reflexes*	Resting Minute Ventilation (cc.)	Tidal Volume (cc.)	Vital Capacity 1st Second (cc.)	Total Vital Capacity (cc.)	Predicted Vital Capacity (%)	Maximal Breathing Capacity	Predicted Maximal Breathing Capacity (%)
1. P. H., male 66 yr.	Control	25	4+	96	154/90	2+	3+	11,150	446	168	1,270	37.2	19.6	20.8
	Morphine Sulfate ¼ gr.													
	15	21	4+	88	140/90	2+	...	.....	...	...	....	....	....	....
	30	21	4+	88	140/90	2+	...	.....	...	...	....	....	....	....
	Morphine Sulfate ¼ gr.													
	45	17	2+	80	130/84	1+	...	.....	...	...	....	....	....	....
	60	16	2+	80	130/90	1+	...	6,656	416	165	1,701	50.0	11.8	12.5
	Nalline, 10 mg. i.v. followed by	..	...	...	.....	...	...	.....	...	...	....	....	....	....
	Nalline, 10 mg. in 300 cc. 5% G/W i.v.	..	...	...	.....	...	...	.....	...	...	....	....	....	....
	Immediate	19	4+	78	130/80	1+	...	.....	...	...	....	....	....	....
	15	18	4+	80	130/80	1+	...	.....	...	...	....	....	....	....
	30	20	4+	74	146/90	1+	3+	.....	...	...	....	....	....	....
	60	19	4+	74	144/90	1+	3+	7,562	398	378	1,465	42.9	17.0	12.5
2. F. P., male, 61 yr.	Control	20	4+	90	206/100	3+	4+	15,758	788	811	1,907	52.4	36.5	38.4
	Morphine Sulfate ½ gr.													
	15	20	4+	100	180/94	3+	4+	.....	...	...	....	....	....	....
	30	20	3+	110	180/100	3+	4+	.....	...	....	....	....	....	....
	60	11	4+	104	170/96	1+	4+	7,184	653	756	1,985	54.5	35.6	37.4
	Nalline, 10 mg. i.v. followed by	..	...	...	.....	...	...	.....	...	...	....	....	....	....
	Nalline, 10 mg. in 300 cc. 5% G/W i.v.	..	...	...	.....	...	...	.....	...	...	....	....	....	....
	Immediate	15	4+	98	190/100	2+	4+	.....	...	...	....	....	....	....
	15	20	4+	104	200/120	2+	4+	.....	...	...	....	....	....	....
	30	16	4+	100	180/100	2+	4+	.....	...	...	....	....	....	....
	60	20	4+	88	180/100	2+	4+	13,620	681	677	1,705	46.9	....	....

* Depth of respiration, size of pupils and tendon reflexes are graded from 4+ to 1+, 4+ indicating normal status and 1+ indicating marked decrease.

including pulmonary ventilation, were performed prior to and during the entire procedure. Response to the administration of nalline was prompt and essentially the same as in the morphine-intoxication cases. The data in Table III show an initial depression, caused by morphine sulfate, of the respiratory rate and resting minute ventilation which were subsequently restored to normal by intravenous nalline in both patients. The circulatory changes were minimal after morphine sulfate and nalline. The vital capacity improved slightly in both patients while the maximal breathing capacity increased in one but decreased in the other. The excitation period following the administration of nalline in these patients was fifteen to twenty minutes, respec-

TABLE IV

EFFECTS OF INTRAVENOUS NALLINE, 10 MG., ON FIVE NON-NARCOTIZED INDIVIDUALS

Patient	Time of Observation (min.)	Respiratory Rate	Depth of Respiration*	Pulse	Blood Pressure	Pupils*	Deep Tendon Reflexes*	Tidal Volume (cc.)	Resting Minute Ventilation (cc.)	Timed Vital Capacity		Predicted Vital Capacity (%)	Maximal Breathing Capacity (L./min.)	Predicted Maximal Breathing Capacity (%)
										1st Sec. (cc.)	Total (cc.)			
1. W. K.; male; 30 yr.	Control: Nalline	17	4+	74	120/64	4+	3+	627	10,659	2,204	4,361	95.6	81.2	54.3
B.S.: 2.11 m²	1	17	4+	74	130/70	1+-2+	3+	...	.....	....	.....	.....	.....	....
	5	13	4+	72	120/64	1+	.....	...	.....	.....	.....	.....	.....	....
	10	13	2+	68	120/64	1+	4+	...	.....	.....	.....	.....	.....	....
	15	13	4+	...	.....	.....	.....	524	6,812	1,984	3,776	82.8	85.2	56.9
	30	12	4+	70	120/70	1+	4+	...	.....	.....	.....	.....	.....	....
	45	12	4+	...	.....	.....	.....	663	7,956	1,645	3,743	82.0	64.6	43.2
	60	15	4+	68	120/68	2+	4+	...	.....	.....	.....	.....	.....	....
	75	15	4+	70	130/70	2+	4+	...	.....	.....	.....	.....	.....	....
	90	16	4+	68	134/70	2+	4+	636	10,176	1,573	3,910	85.7	49.2	32.9
2. W. C.; male; 59 yr.	Control: Nalline	25	4+	88	160/86	2+-3+	3+	567	14,175	1,308	3,738	97.2	51.9	46.7
B.S.: 2.00 m²	1	23	4+	80	150/80	1+-2+	.....	...	.....	.....	.....	.....	.....	....
	5	23	4+	82	160/90	1+	3+	...	.....	.....	.....	.....	.....	....
	10	22	4+	88	160/86	1+	3+	...	.....	.....	.....	.....	.....	....
	15	21	4+	...	.....	.....	.....	471	9,891	1,051	2,570	66.8	33.1	29.7
	30	23	1+	84	150/80	1+	3+	...	.....	.....	.....	.....	.....	....
	45	17	1+	...	.....	.....	.....	485	8,246	1,215	2,406	62.5	61.9	55.6
	60	22	2+	84	150/80	1+	2+	...	.....	.....	.....	.....	.....	....
	75	22	1+	84	150/80	1+	2+	...	.....	.....	.....	.....	.....	....
	90	23	1+	82	150/80	1+-2+	2+	389	8,947	981	2,617	68.0	40.1	35.9
3. W. H.; male; 67 yr.	Control: Nalline	21	4+	96	160/84	3+	3+	775	16,275	479	2,156	57.3	32.0	30.5
B.S.: 1.64 m²	1	21	4+	108	160/90	2+	3+	...	.....	.....	.....	.....	.....	....
	5	19	4+	84	160/90	2+	3+	...	.....	.....	.....	.....	.....	....
	10	21	4+	90	154/88	2+	3+	...	.....	.....	.....	.....	.....	....
	15	14	4+	...	.....	.....	.....	623	8,722	551	2,660	70.7	28.6	27.0
	30	17	4+	86	160/90	1+	3+	...	.....	.....	.....	.....	.....	....
	45	14	4+	108	170/86	1+	2+	496	6,948	479	2,540	67.5	26.6	25.0
	60	15	4+	90	194/100	1+	2+	...	.....	.....	.....	.....	.....	....
	75	19	4+	84	150/90	2+	2+	...	.....	.....	.....	.....	.....	....
	90	20	4+	110	150/90	2+	2+-3+	548	10,960	526	2,653	70.5	36.2	34.5
4. L. H.; female; 43 yr.	Control: Nalline	14	4+	68	132/90	2+	3+	699	9,786	564	2,330	81.0	39.1	47.0
B.S.: 1.63 m²	1	14	4+	64	140/90	2+	3+	...	.....	.....	.....	.....	.....	....
	10	12	4+	56	130/90	1+	3+	...	.....	.....	.....	.....	.....	....
	30	12	4+	...	.....	.....	.....	707	8,484	707	2,195	76.0	38.7	47.0
	45	14	4+	60	130/88	1+	3+	...	.....	.....	.....	.....	.....	....
	60	13	4+	54	130/80	1+-2+	3+	501	6,513	463	2,048	71.0	30.8	37.0
	75	11	4+	...	.....	.....	.....	512	5,632	707	2,487	86.0	36.2	44.0
	90	15	4+	54	140/80	2+	.....	...	.....	.....	.....	.....	.....	....
5. M. K.; male; 27 yr.	Control: Nalline	17	4+	78	120/80	3+	3+	656	11,152	2,353	5,078	116.0	92.3	67.0
B. S.: 1.91 m²	1	14	4+	78	130/90	2+	3+	...	.....	.....	.....	.....	.....	....
	5	11	3+	70	120/84	2+	3+	...	.....	.....	.....	.....	.....	....
	10	11	4+	70	120 80	2+	3+	...	.....	.....	.....	.....	.....	....
	15	9	4+	...	.....	.....	.....	711	6,399	2,571	5,142	118.0	109.9	79.5
	30	11	4+	66	130/86	2+	3+	...	.....	.....	.....	.....	.....	....
	45	11	4+	86	130/80	2+	2+-3+	666	7,326	2,393	4,648	106.0	109.9	79.5
	60	11	4+	86	130/90	2+	2+-3+	...	.....	.....	.....	.....	.....	....
	75	11	4+	72	130/88	2+	3+	722	7,942	2,521	4,214	119.4	113.6	82.2
	115	11	4+	80	110/74	1+-2+	3+	...	.....	.....	.....	.....	.....	....

* Depth of respiration, size of pupils and deep tendon reflexes are graded from 4+ to 1+, with 4+ indicating normal status and 1+ indicating marked decrease.

tively. A close resemblance to the withdrawal syndrome of narcotic addicts was observed, but to a lesser degree.

IV. Three young patients with barbiturate poisoning (suicide attempts) were studied. All three were in coma and their deep tendon reflexes were diminished. Respiratory depression, however, was not present. Respirations were deep and even, with a respiratory rate ranging from 14 to 22 per minute. Nalline was given intravenously in much higher doses (20 to 30 mg.) than usually administered in our previous studies. No beneficial effect was noted from repeated doses and finally other agents were employed. Nalline had no demonstrable toxic effect upon these three patients.

V. Ten to 20 mg. of nalline was given intravenously, in an attempt to hasten awakening, to four patients who had received intravenous pentothal® as an anesthetic for minor operative procedures. The speed of awakening was not increased and nalline failed to improve the mild respiratory depression noted in one of these patients.

VI. The effects of nalline were studied in five symptom-free asthmatic subjects. Control studies including pulmonary ventilation were made in all patients and were repeated following the intravenous administration of 10 mg. of nalline. Marked sedation, myosis and a slight decrease in the respiratory rate and resting minute ventilation were observed in all patients. One of the five patients showed an increase in the timed vital capacity and another a rise in the maximal breathing capacity after intravenous nalline; in the other patients these functions were decreased. (Table IV.) These changes lasted from forty to ninety minutes, except for the sedative effect which was more prolonged. The patients remarked that they felt sleepy and they usually slept soundly for at least two hours. On awakening, no after-effects were noted. One patient complained of nausea and another vomited during the observation period. No significant effects on the circulatory system were observed.

COMMENTS

From the presented data it appears that N-allylnormorphine has different effects in various circumstances. Given to non-narcotized individuals, it acts as a mild depressant upon respiration and to a lesser degree upon circulation. Given after the administration of a toxic dose of opiates, it inhibits or antagonizes their depressant effect, causing a strong respiratory and circulatory stimulation. However strong the stimulating effect in narcotic poisoning, it does not appear to affect the respiratory or circulatory depression caused by non-narcotic agents.

The specificity of nalline is clearly shown in our studies in which it counterated successfully a large variety of natural and synthetic alkaloids, i.e., morphine, demerol, codeine and nisentil.® Its action upon the respiratory depression of narcotized patients is most dramatic. It elevates the previously depressed rate to normal levels in fifteen to thirty seconds after intravenous administration in doses of 5 to 10 mg. and reverses Cheyne-Stokes or irregular breathing consequent to opiate overdosage. Its action is instantaneous and therefore not comparable with that of other analeptic drugs.

The action of nalline upon circulatory depression is more gradual but just as marked. When depression or elevation of the blood pressure is present, it returns to normal levels for that patient within ten to fifteen minutes after the administration of nalline. When the blood pressure has remained within the normal range, no remarkable changes occur.

The action of nalline upon the sedative effect of narcotics is less apparent. The patient becomes more responsive in that there is definite lightening in the depth of sleep and the patient can be aroused more easily. He goes back to sleep, however, if left alone. The degree of this response is largely dependent upon the amount of narcotic given.

There is no ready explanation for the mode of action of nalline upon narcotic-induced poisoning. It seems to be central, as morphine is generally assumed to have a central action. It would appear that the action of nalline is competitive on the basis of its chemical similarity, occupying specific receptors or displacing the narcotic alkaloids from these receptors by chemical competition.[6] Similar competitive action has been reported in a large variety of drugs. This, however, would not explain its action against demerol which has no chemical similarity to morphine.

The optimal dose of the drug has not yet been established. No untoward effects have been observed in our studies from any dose so far employed. In two instances a total of 40 to 60 mg. was given over a period of twenty minutes without ill effect.

Against barbiturate poisoning the administra-

tion of nalline did not appear to be effective. However, it did not increase narcosis and in our studies the patients' general condition did not worsen.

Further study of the mode of action of nalline is indicated. Light may be thrown on the action of morphine and the possible separation of its analgesic and respiratory depressant effects by a new compound or possibly by combined administration of morphine and nalline may evolve.

SUMMARY

1. Nalline has been found to be a safe and reliable specific antidote for narcotic-induced respiratory depression.

2. The action of nalline upon opiate-induced circulatory depression is more gradual but just as marked.

3. Nalline did not appear to be effective against barbiturate intoxication.

4. In non-narcotized individuals nalline produced a slightly diminished respiratory rate, minute ventilation and maximal breathing capacity. A sedative effect was experienced by all subjects.

5. We found 5 to 10 mg. of intravenous nalline effective as the initial dose. However, in order to maintain the stimulating effect a slow intravenous drip of an additional 5 to 10 mg. in 5 per cent glucose in water is advisable.

6. The dramatic effect of nalline in opiate intoxication indicates that it should be available for emergency use in all emergency wards, operating rooms and in the bag of the practicing physician.

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The Use of Primaquine for the Treatment of Malaria in Korean Veterans*

JOSEPH GENNIS, M.D., BERNARD STRAUS, M.D., MICHAEL KENNEY, M.D. *and* BERNARD KLEIN, PH.D.

Bronx, New York

CONSIDERABLE progress was made in the therapy of relapsing Plasmodium vivax malaria following the outbreak of World War II. The increasing military activity of this country in areas with endemic malaria, such as Korea, has spurred investigation into the treatment of this disease. The exposure of large groups of non-immune persons to infection with P. vivax posed several problems. The first and most urgent was the military necessity of maintaining troops in action in these endemic areas. Another was the question of treatment of infected troops returning to the United States.

There are three essential approaches to the treatment of malaria: suppression of the clinical manifestations of the disease, treatment of the acute attack of the infection, and therapy directed at elimination of relapses or radical cure of the disease.

The therapy of P. vivax malaria presents a greater problem than the treatment of other forms of malaria because of the greater tendency toward persistence of the infection. This parasite has adapted itself more effectively to the human host. Following inoculation by an infected mosquito the parasite disappears from the peripheral blood for approximately one week. At the end of this time blood forms or trophozoites appear, causing the primary attack. Following subsidence of this attack a persistent tissue phase develops from which trophozoites are released intermittently into the blood, producing the periodic relapses in this disease.

There are thus three phases of this infection, which have been described as the pre-erythrocytic phase, the erythrocytic phase and the exo-erythrocytic or tissue phase. Shortt has demonstrated that both the pre-erythrocytic phase and the exo-erythrocytic phase occur in the liver cells of mammals.[1,2]

The suppression of P. vivax malaria and the elimination of clinical manifestations of the disease can be attained by eradication of the erythrocytic phase of the infection. The radical cure of this disease, however, can be effected only by destruction of the exo-erythrocytic or tissue forms of the parasite.

At the beginning of World War II quinine was the drug of choice in the treatment of malaria. Because of enemy action this drug was in short supply. Early studies therefore were directed at developing an adequate substitute. Quinacrine (atabrine) had been known since 1930 but was not used widely. It was found to be effective against the erythrocytic phase of P. vivax malaria and more satisfactory than quinine both as a suppressive and for treatment of the acute attack.[3] Quinacrine was employed extensively during and after World War II. However, it is ineffective against the exo-erythrocytic phase of the disease and has no effect on the relapse rate of P. vivax malaria. It also has significant toxicity manifested by skin discoloration, atypical lichen planus lesions, agranulocytosis and aplastic anemia.

Following World War II newer and more effective agents against the erythrocytic phase of P. vivax were found. Chloroquine, a 4-amino-quinoline derivative, was developed in this country.[4,5] British investigators[6] developed paludrine,® a synthetic biguanadine compound. Chloroquine has proved to be highly effective both in the suppression and treatment of the acute attack of malaria. Both drugs are relatively non-toxic. These newer agents, however, also are ineffective against the exo-erythrocytic phase of the parasite and do not affect the relapse rate.

The military problem of suppression of malaria and the clinical problem of treatment of

* From the Medical and Laboratory Services of the Veterans Administration Hospital, Bronx, N. Y.

the acute attack have been adequately solved by these agents. Chloroquine has been used effectively as suppressive therapy in Korea in a dosage of 0.5 gm. once weekly. For treatment of the acute clinical manifestations of P. vivax malaria, 2.5 gm. of chloroquine diphosphate given in a three-day period are highly successful. The problem of developing a drug effective in achieving a radical cure of this disease has received considerable study.

In any study directed at eliminating the exo-erythrocytic phase of P. vivax malaria the strain differences existing in this species of parasite must be carefully considered. P. vivax is a highly adaptable organism that varies considerably depending upon the area in which it is endemic. These strain differences affect the relapse rate of this disease. P. vivax malaria as encountered in the Southwest Pacific area has a relapse rate of about 80 per cent. On the other hand, the same infection occurring in the Mediterranean area[7] has a relapse rate of only 30 per cent. Other strain differences are manifested in the length of the latent period. Temperate zone P. vivax malaria as it exists in Korea has become adapted to the long winters by developing a more prolonged tissue phase. Clinically, this manifests itself in a long latent period averaging six to nine months. This differs from tropical zone P. vivax malaria in which the latent period may be as short as thirty to forty-five days.[8]

A radical cure of P. vivax malaria was suggested by the studies of Sinton and Bird[9] and Jarvis[10] using pamaquine (plasmochin®) and quinine concurrently. They obtained significant reduction in the relapse rate, presumably as a result of eradication of the tissue or exo-erythrocytic phase. These observations were confirmed by Kelleher and Thompson,[11] Berliner[12] and Most.[13] Quinine was employed with pamaquine because it apparently potentiates the action of the latter drug.

Most et al.[13] employed dosage levels of 60 mg. of pamaquine naphthoate and 2 gm. of quinine sulfate daily for fourteen days. They found a significant reduction in the relapse rate on this regimen, without serious toxic manifestations. Berliner et al.[12] used a higher dosage level of pamaquine, 60 to 90 mg., together with 2 gm. of quinine daily for fourteen days and observed that pamaquine had a curative action in sporozoite-induced Chesson strain vivax malaria. They concluded that curative effects observed at lower dosage levels are attributable to greater strain susceptibility, to treatment of a later stage of the disease or to a lesser density of the underlying tissue infection.

Pamaquine when employed at higher dosage levels (above 60 mg.) has significant toxicity which is serious enough to limit its usefulness. The toxic manifestations include anorexia, epigastric pain, abdominal cramps, nausea, vomiting, diarrhea, cyanosis and circulatory disturbances such as dyspnea and hypertension. There are T-wave changes in the electrocardiogram, methemoglobinemia, hemolytic anemia, headache, dizziness, psychosis and coma. In colored races hemolytic phenomena are especially frequent.

From the beginning of World War II to the present, the Board for Coordination of Malarial Studies of the National Research Council investigated thousands of drugs in an attempt to secure an agent more effective than pamaquine against the exo-erythrocytic phase of P. vivax and one which also was less toxic. Alving conducted clinical trials of eighteen pamaquine analogs of the 8-amino quinoline structure.[14] Pentaquine, 6-methoxy-8-(5-isopropylamino-pentylamino) quinoline, was studied most extensively.[15,16] Quinine potentiates the action of pentaquine in a manner similar to its effect with pamaquine. The toxicity of pentaquine moreover is decreased by the concurrent administration of quinine.[17] Alving[15] found that 60 mg. of pentaquine base were approximately equivalent to 90 mg. of pamaquine base in its effect on the relapse rate.

Studies demonstrating the effectiveness of pentaquine in returning infected veterans have been reported by Coggeshall[18] and by Straus and Gennis.[19,20] Using only 30 mg. of pentaquine base and 2 gm. of quinine, Straus and Gennis observed a striking reduction in the relapse rate of P. vivax malaria, to only 2 per cent. A control group using alternate cases, treated with chloroquine alone, had a relapse rate of 34.6 per cent. At the dosage level of pentaquine employed, toxic manifestations were minor.

Isopentaquine, 6-methoxy-8-(4-isopropylamino-1-methylbutylamino) quinoline, has been shown experimentally to be more effective and less toxic than pentaquine. Extensive clinical trials of this agent, however, have not been reported.

Primaquine, 6-methoxy-8-(4-amino-1-methylbutylamino) quinoline, was studied during the Korean war. Its structural relationship to other

quinoline analogs is shown in Figure 1. Preliminary reports indicating its effectiveness have been made by Alving et al.[8] These reports indicate that primaquine is more effective against the exo-erythrocytic phase of P. vivax malaria than either pentaquine or iso-pentaquine, and that it is less toxic.

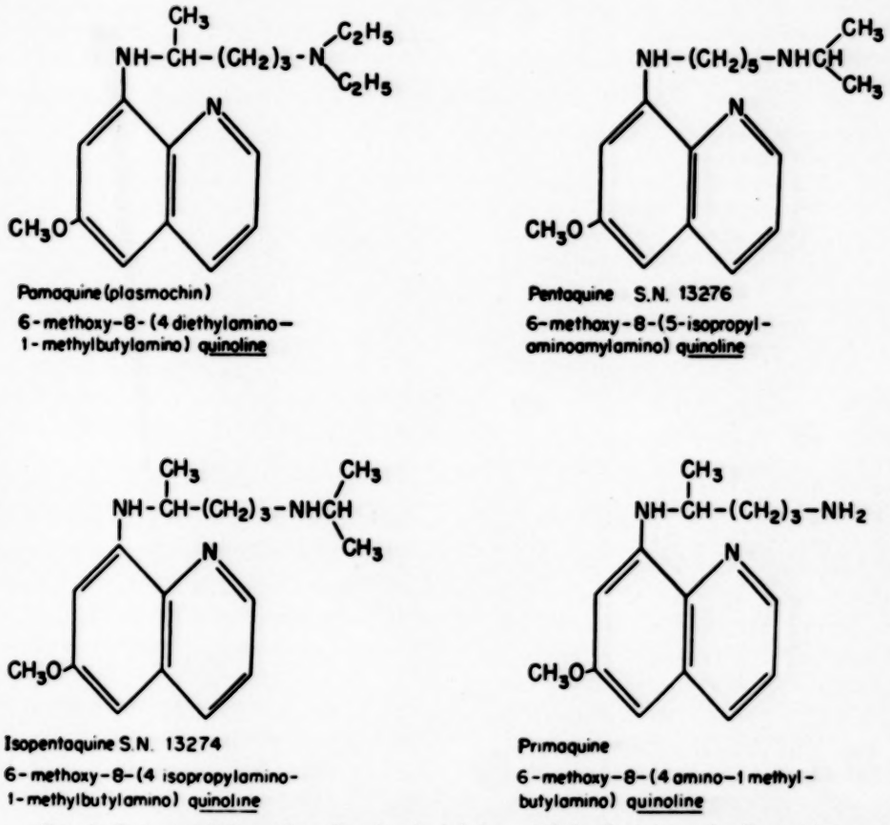

FIG. 1. Structural formulas of antimalarial drugs of the 8-aminoquinoline series.

In 1951 the present study was begun to determine the effectiveness of primaquine in the radical cure of relapsing P. vivax malaria. In order to determine not only the effectiveness of this agent against the exo-erythrocytic phase but also its possible effectiveness against the erythrocytic phase of the infection, therapy was limited to primaquine alone.

METHODS

The methods followed in this study are outlined in Table I. All patients showed characteristic clinical evidence of malaria. A positive smear for P. vivax was essential for inclusion of the patient in the study. Treatment consisted of 15 mg. of primaquine base given once daily after a meal, for fourteen days. Laboratory studies included daily thick and thin blood smears for malaria until three negative smears were obtained, electrocardiogram before therapy and at the conclusion of therapy, urinalyses and complete blood counts twice weekly, methemoglobin determinations twice weekly, a cephalin flocculation test and serum bilirubin determination prior to treatment and at the conclusion of treatment. In patients of the colored races a daily hemoglobin estimation and examination of the urine daily for hemolysis were done. Patients were observed during treatment for evidence of toxicity. Following discharge of the patients from the hospital they were examined at monthly intervals, at which time thick and thin blood smears for malaria were studied to determine possible recurrences.

RESULTS

Table II shows the data of the patients studied. There were 101 patients who received treatment with primaquine. Of these all were white except two who were Negro. The average interval to relapse which was estimated from the date of leaving the endemic area to the onset of the initial attack was seven months. This correlates

well with studies reported by Alving.[8] Following treatment the patients' temperatures usually became normal on the second day. In many patients there was a chill and a rise in temperature on the day following onset of treatment. Blood smears became negative for P. vivax on about the fourth day of treatment. The duration of the average follow-up period was 12.2 months.

TABLE I
METHOD OF PRIMAQUINE STUDY

1. Clinical evidence of malarial relapse
2. Positive smear for P. vivax
3. Therapy. primaquine base 15 mg. once daily p.c. for 14 days
4. Laboratory data: Daily smear until 3 negatives obtained
   ECG before and after therapy
   Urinalysis, complete blood count twice weekly
   Methemoglobin determinations twice weekly
   Cephalin flocculation test, serum bilirubin before and after therapy
   Colored races—daily hemoglobin; observation of urine daily for hemolysis
5. Toxicity study
6. Examination and blood smears to determine relapses once monthly

Primaquine therapy proved to be rapidly effective and highly satisfactory in the overwhelming majority of patients treated. However, one relapse and four recrudescences occurred in the 101 patients treated. Recurrences are analyzed in Table III. They have been broken down into two groups: relapses and recrudescences. A relapse is a recurrence of the disease which appears thirty days or more following completion of therapy. It is attributable to failure of the drug to eliminate the tissue phase of the malarial parasite. A recrudescence of the disease occurs within thirty days following completion of therapy. It is due to the relatively weak effect of the drug on the trophozoites of the erythrocytic phase and does not signify failure of the drug to eliminate the tissue phase. Only one relapse was observed. This occurred sixty days following treatment. There were four recrudescences occurring at five, nineteen, twenty and twenty-three days following treatment. All recurrences of malaria were treated with chloroquine alone. None has subsequently relapsed during the period of observation.

TABLE II
ANALYSIS OF PATIENTS STUDIED

No. of treated cases	101
White	99
Colored	2
Average interval to relapse	7.1 mo.
Average time to normal temperature	2.1 days
Average time to negative smear	4.3 days
Average follow-up period	12.2 mo.

Table IV shows the observations on the toxic manifestations of primaquine. These are compared with the toxic manifestations we observed in a previous study with pentaquine and quinine.[20] It is apparent that primaquine in the dosage employed has no significant toxicity. Nausea, abdominal pain, dizziness, tinnitus, vomiting, fever and headache were not observed although they were present to a moderate degree during therapy with pentaquine and quinine. Methemoglobinemia was not a prominent feature at the dosage levels of primaquine used. It presented no problem as a toxic manifestation. The average peak of methemoglobinemia observed over the entire course of treatment was 0.95 gm. per cent with a range of 0.3 to 2.8 gm. per cent. After cessation of therapy the methemoglobin returned to pretherapy levels rapidly.

TABLE III
ANALYSIS OF RESULTS

	Number	Per cent	Interval to Relapse or Recrudescence (days)
Relapses	1	1.0	60
Recrudescences	4	4.0	5
			19
			20
			23

TABLE IV
TOXICITY

Toxic Manifestations	Pentaquine-Quinine	Primaquine
Nausea	30%	0
Abdominal pain	28%	0
Dizziness	20%	0
Tinnitus	18%	0
Vomiting	18%	0
Fever	14%	0
Headache	12%	0
Methemoglobinemia		
Average peak	....	0.95 gm. %
Range	....	0.3–2.8 gm. %

Since malaria is a hemolytic disease, moderate anemia was not infrequently observed. In no case, however, could the anemia be related to drug toxicity. In one Negro patient marked anemia developed during the first week of therapy. Primaquine was discontinued as a precautionary measure after six days. Manifestations of malaria, including a positive smear, recurred nine days later. Primaquine was again administered in the usual dosage for the full period of fourteen days without recurrence of anemia. It was concluded that the anemia observed was related to the hemolytic effect of the disease rather than to drug toxicity.

The occurrence of biologic false-positive serologic tests for syphilis in malaria is well known. Serologic tests in the present study, using the V. D. R. L. flocculation test, were positive in only 11 per cent of patients. In all patients except one the Kolmer-Wassermann test was negative. One patient had a positive V. D. R. L. test and a positive Kolmer-Wassermann test. The Kolmer-Wassermann in this case became negative without specific therapy within seventeen days. These findings differ from those observed in a previous study involving predominantly patients with malaria which originated in the Southwest Pacific area.[19,20] In that study, using the Kolmer-Wassermann and Kahn as serologic tests, 64 per cent of patients with malaria had positive reactions with one or both tests.[21] These observations may represent another example of strain differences in P. vivax malaria. The significance of these findings will be the subject of a separate report.

There were three patients in whom the acute attack of malaria was associated with an acute exacerbation of chronic glomerular nephritis. There was one patient who manifested evidence of hypersplenism including severe leukopenia and a considerably enlarged spleen. Following therapy for malaria the signs of hypersplenism gradually receded. Thrombocytopenic purpura was observed in another patient during a recrudescence of malaria two weeks following primaquine treatment. The recrudescence was treated with chloroquine. Following this treatment the patient was again treated for four days with primaquine. No further evidence of thrombocytopenic purpura was observed.

COMMENTS

The results indicate that primaquine is a highly effective and relatively non-toxic agent which is active in eliminating the tissue phase of P. vivax malaria. In view of the recrudescences which occurred it is evident that primaquine is not as effective as chloroquine against the erythrocytic phase of the parasite. There is also a greater tendency for the patient to have another chill following the onset of treatment with primaquine than is observed with chloroquine. The optimum regimen for relapsing P. vivax malaria should therefore include the concurrent use of an agent effective against the erythrocytic phase, such as chloroquine, and an agent effective against the exo-erythrocytic phase, such as primaquine. The recommended regimen is chloroquine diphosphate in an initial dose of 1.0 gm. followed in six hours by 0.5 gm. On the second and third days 0.5 gm. is given for a total of 2.5 gm. Primaquine is given in a dose of 15 mg. of the base once daily for fourteen days.

In previous studies with pamaquine, pentaquine and isopentaquine, a second agent such as quinine was given on the basis of experimental data indicating that quinine acted synergistically with and potentiated the action of the 8-aminoquinoline drug. There was evidence which indicated that neither quinacrine nor chloroquine acted in this manner when given with these drugs.[15] The use of chloroquine in association with primaquine, however, is based not upon any synergistic or potentiating action but upon their different sites of action. The use of chloroquine alone in the treatment of the recrudescences was based on the supposition that the tissue phase of the parasite had previously been eliminated by primaquine. The fact that none of the patients who had recrudescences relapsed after chloroquine therapy confirms this opinion. Chloroquine alone was used in the treatment of the relapse to determine the number of recurrences in a primaquine failure. None was observed. Several of our patients had received prophylactic treatment with primaquine during their return voyage to the United States. This was part of an Army study in which placebos and primaquine were employed. We attempted to secure the specific data on our patients. This did not prove feasible as individual records were not available. The military services were routinely treating all personnel returning from Korea with primaquine while on board transport ships. This program of primaquine therapy should effectively reduce the incidence of relapsing P. vivax malaria seen in this country. However, since many veterans returned by airplane

or for one reason or another did not receive or take the full course of therapy, new cases of malaria and relapses of malaria continue to occur in this country.

SUMMARY AND CONCLUSIONS

1. Primaquine was employed in the treatment of P. vivax malaria in 101 veterans of the Korean conflict.

2. There was one relapse with this therapy. Recrudescences were observed in four patients.

3. Toxic manifestations to primaquine at the 15 mg. dosage level employed were negligible.

4. Primaquine is highly effective in the radical cure of P. vivax malaria.

5. In the treatment of an acute attack of P. vivax malaria chloroquine should be given with primaquine to eliminate the manifestations of the disease more rapidly and to prevent recrudescences.

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Reviews

Diphtheria*

A Study of 1,433 Cases Observed during a Ten-year Period at the Los Angeles County Hospital

MORRIS J. NAIDITCH, M.D. *and* ALBERT G. BOWER, M.D.
Beverly Hills, California *Pasadena, California*

THIS paper presents an analysis of 1,433 cases of diphtheria admitted to the Communicable Disease Unit of the Los Angeles County Hospital during the ten years ending June, 1950, and a comparative study of the relevant literature on this disease.

The decreasing incidence of diphtheria in Los Angeles County[71] in the last thirty years parallels the steady decline of the disease throughout the United States. From a maximum of 293.9 cases per 100,000 population in 1924 the incidence declined to 6.7 in 1940. During World War II cases in this county increased moderately to a maximum of 13.8 per 100,000 population in 1944, with a subsequent rapid decline to 1.7 per 100,000 in 1949. These changes are reflected in the number of patients admitted to the Communicable Disease Unit of the Los Angeles County Hospital from 1940 to 1950. In 1941 there were 143 admissions, with a maximum increase to 240 during 1944, a steady decline to 37 in 1949 and only 7 in the first six months of 1950.† The increase from 1940 to 1945 was minimal in this country compared to Europe,[52] especially in countries occupied by German Forces, where in some instances it exceeded a hundredfold.[38,106]

A total of 1,433 patients with clinical diphtheria, bacteriologically proven, were admitted to the Communicable Disease Unit during the ten years from July 1, 1940, to June 30, 1950. A history of previous attacks of diphtheria was obtained from fourteen patients, contrasted to thirty-one of 403 patients reported by Ammundsen et al.[4]

† Nineteen patients were admitted in the twelve months ending in June, 1951, and only two in the next twenty-four months.

AGE

Age incidence is shown in Table 1; 57.7 per cent of the patients were less than ten years old, closely approximating the figure of 61 per cent of 752 cases reported from this hospital in 1942.[107] From July, 1940, to December, 1944, 59.8 per cent of the patients were less than ten years old and 13.8 per cent were thirty years or older; from January, 1945, to June, 1950, 53.2 per cent were less than ten years old, while 18.7 per cent were thirty years or older. However, the statistical study of age trends by the Los Angeles County Health Department[29] showed only minimal changes in the younger age groups during the seventeen-year period preceding 1948. This is reflected in the experiences of widely different geographic centers: Kentucky[23] shows little change in the period from 1932 to 1946; in New York State[56] the relative occurrence in the younger age groups over a twenty-two-year period to 1939 shows minimal changes; 81.9 per cent of 41,665 cases reported from Montreal[14] from 1887 to 1943 were below ten years of age; in the eleven years from 1936 to 1946, only 21.1 per cent of 31,519 cases in Glasgow[21] were over fifteen years of age; in 1945, 30.9 per cent of cases reported from the United Kingdom[109] were above fifteen years.

Recent reports, however, show a trend toward greater incidence in the older age group: in Massachusetts,[33] 44 per cent were over fifteen years of age in an epidemic during 1945; of 210 cases in Minneapolis[99] 46 per cent were over fifteen years of age between 1937 and 1947; of 403 patients in Stockholm[4] 70 per cent were over fifteen years of age in 1943 and 1944. McLeod's review[78] also shows a shift in the maxi-

* From the Communicable Disease Service, Los Angeles County Hospital, Los Angeles, Calif.

mum incidence from the one to five year group to the school age child. The preponderance of cases among adults becomes even more evident in studying several recent large epidemics. Of the 3,538 cases reported in a five-month period ending February 28, 1946, from Land Oldenburg, Germany,[109] 60.9 per cent were over fifteen years; 45 per cent of 1,028 cases were over fifteen years in the Halifax epidemic[43] of 1940 to 1941; 68 per cent of the 1,754 cases in Copenhagen[106] during 1945 were fifteen years or older, in contrast to a four- to six-times greater incidence in previous years in patients under fifteen years as compared to the older age group.

Goebel and Ströder[46] note an exception to this trend and report an increase from 5 per cent in patients less than one year of age to approximately 20 per cent from the fall of 1945 to the summer of 1947, with the mortality rate increasing from 10 per cent to 36 per cent. Among the 109 cases under one year of age were fifty-nine infants less than one month old with a 44 per cent mortality rate.

Most reports indicate a high mortality rate in diphtheria in infancy, with a predilection for localization in the nares.[85,102,107] Usually the incidence in the first year of life is recorded as 5 per cent or less.[87] One of the youngest patients reported was a four day old infant.[85] Signs of enteritis and pneumonia are frequent in infants but myocarditis and neuritis rarely develop.[102] Our series of 1,433 cases included nineteen patients less than one year old, an incidence of 1.3 per cent; nine were less than six months, and two under a month, namely, an eight day old infant with diphtheria of the umbilicus and a two week old infant with bilateral diphtheritic conjunctivitis.

TABLE 1

AGE, SEX AND MORTALITY RATES OF 1,433 DIPHTHERIA PATIENTS AT THE LOS ANGELES COUNTY HOSPITAL

Age (yr.)	Males			Females			Total No. Males and Females			
	No. Patients	No. Deaths	Mortality (%)	No. Patients	No. Deaths	Mortality (%)	No. Patients	Per cent of 1,433 Patients	No. Deaths	Mortality (%)
0–1	10	3	30.0	9	0	0	19	1.3	3	15.8
1–5	241	23	9.7	169	23	13.6	410	28.6	46	11.2
5–10	217	27	12.4	181	15	8.3	398	27.8	42	10.5
10–20	96	2	2.1	111	5	4.5	207	14.4	7	3.4
20–30	59	1	1.7	114	1	0.9	173	12.1	2	1.2
30–40	62	10	16.1	42	2	4.8	104	7.3	12	11.5
40–50	49	14	28.6	19	1	5.3	68	4.7	15	22.1
50 plus	36	9	25.0	18	1	5.6	54	3.8	10	18.5
Total	770	89	11.6	663	48	7.2	1433	....	137	9.6

SEX

Most reports[21,23,56,67,75,109] show greater incidence in the female. Usually only in patients less than five years of age and in the older age groups does the male incidence exceed that of the female.[109] However, in the series reported from San Francisco[17] and in our group there is a greater male incidence (65 per cent of 273 and 54 per cent of 1,433 patients, respectively). Only in the ten to thirty year age group in our present series is there a predominance of females (59 per cent of 380 patients). The males again show their greatest incidence in the young (59 per cent of 429 patients under five years of age) and older groups (60 per cent of 104 patients between thirty and forty years, 72 per cent of 68 patients between forty and fifty years, and 67 per cent of 54 patients over fifty years of age).

SEASONAL INCIDENCE

The monthly distribution in our series is as follows: January, 10 per cent; February, 11.5 per cent; March, 7.6 per cent; April, 6.2 per cent; May, 7.3 per cent; June, 7.8 per cent; July, 6 per cent; August, 6.6 per cent; September, 8.3 per cent; October, 12.1 per cent; November, 8.9 per cent and December, 7.6 per cent. These figures

are in accord with the generally found increase in colder seasons, though the difference is not as pronounced as those Ben-Shabetai[13] reported, 75 per cent of his cases occurring from November to February inclusive, and in Choremis' report[27] 66 per cent of 551 cases occurred between October and January.

A moderate increase during the winter months was apparent in our series in the one to five and twenty to thirty year age groups. However, an abrupt two- to threefold increase was noted in school age children in the three months following the opening of school in September. The incidence in patients over thirty years was significantly greater in the first as compared to the last six months of the year, with the smallest quarterly incidence occurring in the months of September, October and November.

In discussing the seasonal incidence of diphtheria, Wildführ's findings[112,113] are of interest. In a study of 15,000 sera he found the antitoxin content of the blood to be lowest at the start of winter, which he believes to be the principal cause for the higher incidence of the disease during the colder seasons. In addition, studies on 3,000 patients appeared to show that the response to immunization by these patients also was diminished during winter.

MORTALITY RATE

Our mortality rate in 1,433 cases was 9.6 per cent, 137 patients dying from the disease. There were two whose deaths were not directly due to diphtheria, two who were dead on arrival at the hospital and forty-four who died within twenty-four hours of admission. Excluding these, the corrected mortality rate is 6.4 per cent.

Mortality rates reported in various series in the literature are recorded in Table II. In Los Angeles County[71] it has varied from 3.5 to 6.8 per cent during the period from 1918 to 1939, and from 5.6 to 11 per cent during the subsequent nine years. In the United States as a whole, however, there has been a definite trend to a decreasing rate during the latter part of the same period.

Age. Mortality was greatest in the youngest and oldest age groups, the lowest being in the ten to thirty year group. (Table I.) Most studies[14,22,29,41,43,56,57,106,107,109] agree on the appreciably greater mortality in younger patients, the disease being particularly virulent in the first few months of life. The 1945 figures from England and Wales[106] reveal a 10.3 per cent fatality rate in patients less than two years of age, 1.4 per cent in the fifteen to twenty-four year age group and 3.8 per cent in patients over twenty-five years. O'Regan et al.[85] reported an epidemic of diphtheria in nine newborns with a 100 per cent death rate. Stammler[102] reported 160 cases, 50 per cent being less than three months of age, with a mortality of 50 per cent. Goebel and Ströder's series[46] with a 44.1 per cent mortality in the first month of life has already been mentioned. Rolleston[95] in 1910 recorded a fatality rate of 36.8 per cent in seventy-six infants less than one year old. A 20 per cent rate in neonatal and nursing infants was recently reported from Norway and Sweden.[87]

Other authors[29,109] have also noted a higher death rate in the very old.

Sex. The mortality rate of 11.6 per cent in 770 males in our series is appreciably greater than the 7.2 per cent rate in 663 females. The New York statistics[56] from 1921 to 1945 show a 7.6 per cent rate in 19,835 male and 6.4 per cent in 22,690 female patients. The Oldenburg, Germany epidemic[109] of 1945 to 1946 revealed fatality rates of 6.4 per cent in male and 4.6 per cent in female patients, and the recently reported San Francisco figures[17] show rates of 20.2 per cent in male and 17.8 per cent in female patients.

A further breakdown of our mortality figures shows the rate to be 10.4 per cent in male and 12.9 per cent in female patients under five years of age and 9.2 per cent in male and 6.8 per cent in female patients between five and twenty years of age. The greatest variation, however, was apparent in patients over thirty years of age, with rates of 22.4 per cent in 147 males and only 5.1 per cent in 79 females. Even excluding deaths in patients with chronic alcoholism, in whom the mortality was approximately three times the general rate, a marked difference is still present in this older age group (13.6 per cent in the males and 2.6 per cent in the females).

Mortality Rate in Relation to the Interval between Onset of Disease and Administration of Diphtheria Antitoxin. Of the 1,400 cases in which such information was available, 16.8 per cent were treated within the first twenty-four hours of the disease; 17.8 per cent in the second day; 19.5 per cent in the third; 14.5 per cent in the fourth; 11.2 per cent in the fifth; 4.6 per cent in the sixth; 8.0 per cent in the seventh; and 7.4 per

cent in eight or more days after the recorded onset of the disease. Since the exact hour of onset was rarely recorded, time indicated by the above figures must be approximate. Mortality rates based on the day of the disease in which the comparative mortality figures: first day, 0.0 per cent; second, 4.0 per cent; third, 16.1 per cent; fourth, 17.6 per cent; fifth, 20.0 per cent; sixth, 21.4 per cent; and after the sixth day, 29.9 per cent.

TABLE II

DIPHTHERIA MORTALITY RATES AS RECORDED IN THE LITERATURE

Locale	Year	No. Cases	Mortality (%)	
Poland[106]	1946	22,412	5.0	
Germany[106]	1939	150,000	3.8	
	1942	237,000	5.0	Increased no. of malignant cases
Hungary[106]	1940	4,927	5.5	
	1946	9,576	12.0	Insufficient DAT and immunization
Naples, Italy[108]	1938–1947	6,242	4.7	
England[52]	1935–1939	59,114	4.8	
	1945	18,596	3.8	
	1946	12,337	3.8	
Gateshead, U. K.[50]	1936–1943	2,278	5.4	
Scotland[91]	1941–1942	17,091	4.7	Non-immunized patients
		2,833	0.5	Immunized patients
[60]	1943	2,521	4.0	Non-immunized patients
		825	0.6	Immunized patients
[106]	1946	.....	1.8	
Glasgow[22]	1934–1942	11,313	4.0	(Approx.)
[21]	1932–1946	17,832	3.8	
U. K. Army[86]	1944	534	2.4	
Ireland[84]	1943–1944	125	2.4	Predominantly gravis
Stockholm[94]	1941–1947	3,500	4.0	
Netherlands[105]	1942–1944*	150,000	7.0	
Copenhagen[57]	1945	1,754	9.7	54% gravis
Athens, Greece[27]	1946–1947	551	5.8	All children
Land Oldenburg, Germany[109]	Oct. 1945 to	1,242	6.4	Male
	Feb. 1946	2,296	4.6	Female
Montreal[14]	1887–1889	3,758	45.6	
	1930–1934	2,785*	9.2	
	1943	158	17.1	
Halifax[60]	1940–1941	891	2.5	
[43]	1940–1941	1,028	4.3	
New York State[56]	1921–1945	42,525	7.0	
New York City[20]	1933–1938*	3,220	5.5	
Boston[59]	1895–1920	33,513	10.4	
	1921–1946	5,478	9.9	
Baltimore[34]	1943	106	2.8	
	1944	144	6.3	
Illinois-Urban[67]	1936–1940	.....	10–14.8	
Rural	1936–1940	.....	7.2–8.8	
Chicago[55]	1928–1932	4,671	11.7	
San Francisco[17]	1942–1950	273	19.3	
Los Angeles[107]	1938–1940	753	4.8	
	1940–1950	1,433	9.6	

* Approximate figure.

first specific therapy was given were as follows: first day, 4.2 per cent; second, 5.2 per cent; third, 9.2 per cent; fourth, 10.8 per cent; fifth, 13.4 per cent; sixth, 12.3 per cent; seventh, 12.5 per cent; eight or more days, 20.2 per cent. The San Francisco cases[17] show the following

The median day of entry of both males and females in the one to ten and ten to thirty year age groups was approximately 2.5. In patients over thirty years, however, the median day for females was 2.5 and for males 3.5 The per cent of patients over thirty receiving treatment five or

more days after the onset of their disease was twenty-eight for the female and forty for the male group, again demonstrating the greater delay of the adult male in receiving therapy.

Race. Of the eighty-eight Negro patients in our series, constituting 6.1 per cent of all patients, four died, a mortality rate of 4.5 per cent. Cases were divided equally among the sexes. Of the forty-six patients less than ten years of age 56.6 per cent were male, whereas 60 per cent of the thirty patients over twenty years of age were female. During the ten-year period of this study there was an approximate 7.5 per cent colored population in this county.

The lower incidence and mortality in the Negro as compared to Caucasian patients has been reported by others. The San Francisco series[17] included a 2.9 per cent incidence in Negro and 1.1 per cent in Chinese patients, compared to an actual population incidence of 7 per cent Negro and 2.5 per cent Chinese. In the cases reported from Kentucky[23] in 1945 to 1946, 3 per cent were in Negroes who constituted 8 per cent of the general population, the relative attack rate being estimated at 1.8 for whites and 1.2 for colored per 100,000 population. In a study of 221 fatal cases of diphtheritic myocarditis reported from the United States Army,[49] 7.2 per cent were non-white in comparison to an approximate 10 per cent non-white population. Martin and Arena's statistics[76] from North Carolina show that the incidence of clinical diphtheria in Negro children was 69 per cent of that in white children; the percentage of positive Shick tests in hospitalized patients was 11.6 per cent in colored compared to 15.4 per cent in white children, and for 1938, a mortality rate per 100,000 population in patients less than fifteen years of age was 143 for white and 28 for Negro children.

Immunization History. Our immunization records were inadequate for accurate statistical study. Numerous reports in the literature indicate marked differences between immunized and non-immunized individuals in the relative incidence and severity of diphtheria and its mortality rates.[4,41,56,57,58,106] Carter's two published series from Glasgow[21,22] show a fatality rate in one series of 4.5 per cent in 1,270 non-immunized and 1.1 per cent in 357 immunized patients, and in the other series, 3.6 per cent in 5,956 non-immunized and 0.3 per cent in 1,638 immunized patients. Among 1,028 patients in the Halifax epidemic[43] 250 had been immunized or were Shick test negative, with a mortality rate of 2 per cent as compared to 5 per cent in the non-immunized groups. In 54,985 immunized individuals in Liverpool[44] from 1925 to 1939 there were 396 cases of diphtheria of whom eleven died, a mortality rate of 2.8 per cent; the case rate in patients less than ten years of age for the years 1933 to 1939 was 11.3 in the uninoculated as compared to 1.5 to 3 per 1,000 population per annum in the immunized group; in persons over ten years of age the rate was found to be somewhat similar in the two groups. In 2,521 diphtheria cases in non-immunized individuals in Scotland[60] there was a mortality rate of 3.9 per cent compared to 0.6 per cent in 825 immunized patients. Ramon[91] emphasizes the value of adequate immunization in his review of the statistics from Scotland where 4.6 per cent of 17,091 non-immunized patients died during 1941 and 1942 compared to 0.5 per cent of 2,833 previously immunized patients. The Danish figures also show that 22 per cent of the non-immunized patients, 5 per cent of those with incomplete immunization, and only 2 per cent with a full course of immunization had malignant diphtheria, with no fatalities in the latter group. Brincker's figures,[50] comparing immunized and non-immunized children, show the comparative incidence of the disease to be 1 to 5.6, and the mortality 1 to 11. Karelitz and Moloshok[61] report the occurrence of the disease in 0.96 per cent of 159,802 immunized and 9.7 per cent of 121,543 non-immunized individuals. Interestingly, some immunologic studies[14] indicate an increasing mortality rate as a greater percentage of children become immunized. Godfrey[45] states that an immediate definite decline in the prevalence of diphtheria can be accomplished by the immunization of approximately 30 per cent or more of children less than five years of age in addition to immunizing 50 per cent or more of school age children.

Bacteriologic Types. The incidence of gravis infection was found to be appreciably higher in Los Angeles County than in other areas in California.[12] In determining the bacteriologic types of diphtheria present in over 400 cases tested from this area during the eight years ending in 1948, Beattie found slightly more than 50 per cent to be of the gravis strain.

No data were available in our cases concerning the specific types of diphtheria organisms present. Some of the reports in the literature are

shown in Table III. McLeod's review[78] indicates that gravis causes a more severe form of diphtheria than the mitis type, although so-called malignant diphtheria may not always be due to gravis infections nor does the latter always cause malignant diphtheria. Frobisher[39] showed that many gravis strains were atoxigenic and suggested abolishing the use of the terms gravis and mitis. McLeod states that hemorrhagic phenomena are slightly more common in intermedius than gravis types and are rare in mitis infections. However, a greater tendency for paralytic phenomena and for local destruction to deep tissues is present in gravis infections. It is most interesting that in laryngeal cases mitis was found four times as often as any other strain.

TABLE III
MORTALITY RATES OF VARIOUS STRAINS OF DIPHTHERIA AS RECORDED IN THE LITERATURE

Locale	No. Cases	Mitis (%)	Intermedius (%)	Gravis (%)
Britain[78]	5,794	2.3	8.6	13.3
Manchester[89]	809	0.5 (198)	8.7 (168)	15.0 (443)
Glasgow[21]	17,832	1.8 (2,933)	4.0 (6,422)	4.4 (8,477)
Glasgow-immune[22]	357	2.5	.....	1.1
non-immune	1,270	1.1	2.5	5.7
Copenhagen[57]	.....	.....	.....	.....
non-immune	333	6.8 (103)	8.2 (110)	19.2 (120)
McLeod's review of literature[78]	25,157	2.6 (6,858)	7.2 (6,807)	8.1 (11,492)

TABLE IV
DIPHTHERIA COMPLICATIONS PRESENT IN THIRTY-FIVE OF FIFTY-EIGHT PATIENTS WITH CHRONIC ALCOHOLISM

Complications	Total No.	Recovered	Died
Myocarditis	22	13	9
Pneumonia	17	5	12
Bulbar paralysis	8	8	..
Peripheral paralysis	6	6	..
Laryngeal paralysis	2	2	..
Kidney disease	3	0	3
Encephalitis	1	0	1

Alcoholism. The effect of alcoholism on mortality has received little attention in the literature. Among fifty-eight patients with chronic alcoholism the fatality rate was 29.3 per cent, 31.3 per cent in forty-eight males and 20.0 per cent in ten females. (Table IV.) A contributing factor to the high mortality rate undoubtedly is the delay in starting therapy, only 14 per cent being treated within the first two days whereas 36 per cent did not receive treatment for seven or more days following onset of the disease.

Mortality Rate Related to Clinical Types of Diphtheria. The clinical types of diphtheria encountered, their incidence and mortality rate are shown in Tables V and VI. None of the patients with either primary nasal or laryngeal diphtheria died. Of the 879 patients with only tonsillopharyngeal involvement sixteen died, a mortality rate of 1.8 per cent. When the disease spread from the throat to other areas, the mortality rate rose to 24.3 per cent in 490 cases and appreciably increased as additional areas were involved. (Table V.) In bull-neck cases the fatality rate was 32.6 per cent (16.7 per cent with tonsillopharyngeal involvement alone contrasted to 52.6 per cent in patients with extension).

TABLE V
INCIDENCE AND MORTALITY RATES OF VARIOUS RESPIRATORY TYPES OF DIPHTHERIA

Types	Total No. Patients	No. of Deaths	Mortality Rate (%)
T	879	16	1.8
T N	102	9	8.9
T N L	22	4	18.2
T N L Tr-B	15	13	86.8
T L	123	9	7.3
T L Tr-B	51	28	54.8
B T	98	16	16.3
B T N	36	13	36.1
B T N L	7	3	42.9
B T N L Tr-B	11	10	90.9
B T L	10	4	40.0
B T L Tr-B	11	10	90.9
Pr. N	27	0	....
Pr. L	20	0	....
Pr. L Tr-B	6	2	33.3
Pr. Tr-B	1	0	....

Abbreviations: T—Tonsillopharyngeal
N—Nasal
L—Laryngeal
Tr-B—Tracheobronchial
B—Bull-neck
Pr—Primary

The mortality rate in the non-laryngeal group was 4.7 per cent (2.5 per cent in the patients without and 22.0 per cent in the patients with bull-neck involvement) and in the laryngeal group 29.5 per cent (24.2 per cent in patients without and 67.5 per cent in patients with bull-neck involvement).

CLINICAL TYPES OF DIPHTHERIA

The incidence of the various anatomic types of diphtheria is shown in Table VI. Simple tonsillo-

pharyngeal involvement was present in 61.1 per cent of the entire group compared to 53 per cent in a previous series from this Hospital,[107] 57.8 per cent in the San Francisco study,[17] 60.6 per cent of 670 cases reported from Israel[13] and 48.4 per cent of 551 children reported from Athens, Greece.[27]

TABLE VI

AGE INCIDENCE AND MORTALITY RATES OF VARIOUS ANATOMICAL TYPES OF DIPHTHERIA

Age (yr.)	Pr. N.		Sec. N.		T.		B.		Pr. L.		Sec. L.		Pr. L. Tr-B		Sec. Tr-B.		Pr. Tr-B.		Eye	Ear	Wound		Umbilical	Vaginal
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	A	A	B	A	A
0-1	6	..	2	1	10	3	1	1	2	..	5	2	..	..	3	3	..	..	1	1	..	..	1	..
1-5	12	..	78	16	374	44	44	20	12	..	117	27	4	2	36	19	1	0	2	1	1	..	..	1
5-10	6	..	50	17	387	42	66	22	3	..	65	21	1	0	24	18	..	..	..	1	1	1	..	..
10-20	2	..	19	4	202	7	23	5	3	..	11	4	..	..	3	3	..	..	..	..	1	..	..	..
20-30	1	..	6	1	169	2	16	1	..	..	6	2	1	..	3	2	..	..	..	..	..	..	..	..
30-40	..	..	11	5	103	11	8	1	..	..	15	8	..	..	7	7	..	..	..	1	..	..	..	..
40-50	..	..	12	5	68	15	10	4	..	..	13	8	..	..	7	6	..	..	..	1	1	1	..	..
50 plus	..	..	11	4	53	10	5	2	..	..	13	6	..	..	6	4	..	..	..	..	2	..	..	..
Total	27	..	189	53	1366	134	173	56	20	0	245	78	6	2	89	62	1	0	3	5	6	2	1	1
Mortality (%)	..	..	....	28	....	9.8	...	32.4	..	..	..	31.8	..	33.3	..	69.7	..	..	..	..	....	33.3	..	..

Abbreviations: Pr.—primary; N.—nasal; Sec.—secondary; T.—Tonsillopharyngeal; B.—Bull-neck; L.—Laryngeal; Tr-B.—tracheobronchial; A—total number of patients; B—total number of deaths

In thirty-seven tonsillar diphtheria cases no membrane or exudate was evident at any time. There were two deaths in this group. Five had had previous immunization whereas seventeen had never been immunized. Paley and Truelove[86] found no membrane in 25 per cent of 245 faucial cases, with the same incidence of neurologic complications as in those patients in whom membranes were present. Johnson[59] states that less than one-third of his cases had typical membranes in the throat. Neubauer[82] states that in previously immunized patients the exudate tends to be more follicular and less confluent in appearance and that it spreads slowly, rarely involves the anterior pillars or soft palate, and is more easily removed than in non-immunized patients. O'Regan[84] reports that in immunized patients many of the throats were free of membrane in twenty-four hours, and in the majority in forty-eight hours. Several reports indicate a greater likelihood for the occurrence of diphtheria in patients with chronic tonsillitis and also in individuals who have not had tonsillectomies.[1,34]

Primary nasal diphtheria was found in twenty-seven patients, mainly in the younger age group. The previous study from this Hospital revealed a 6.4 per cent incidence of this condition with a 2.1 per cent fatality rate. Reports of 0.7 per cent of 273 patients with no fatalities,[17] 2.3 per cent of 551 children[27] and 1.5 per cent of 3,000 cases[86] are present in the literature. Nasal involvement most frequently occurred as a secondary upward extension from the throat and had an appreciably higher fatality rate than the primary form.

Primary laryngeal diphtheria occurred in twenty patients, all less than twenty years old. In all laryngeal cases an appreciably higher incidence in the younger age group was apparent. In a total of 150 males with a 30.7 per cent fatality rate and 122 females with a 27.0 per cent rate, 77.2 per cent were less than ten years old, compared to a general incidence of 57.7 per cent. The death rates in this younger age group were 22.8 per cent of 114 males and 27.1 per cent of 96 females compared to 63.5 per cent of 27 males and 30 per cent of 10 females over thirty years of age. Analysis of the monthly incidence in all age groups showed an almost identical occurrence of laryngeal diphtheria in all months of the year. In patients under ten years 26.9 per cent had laryngeal involvement during the cold in contrast to 23.1 per cent in the warmer months.

Tracheobronchial diphtheria, usually a downward extension from faucial or laryngeal involvement, occurred in ninety-six patients with a mortality rate of 66.7 per cent; 71.8 per cent of these cases were under ten years, the fatality rate being 60.9 per cent.

Bull-neck diphtheria, equally involving both

sexes, occurred in 173 patients with a fatality of 32.4 per cent. The death rate in males, however, was greater than in females (35.4 to 28.6 per cent). A higher incidence in younger patients again was apparent although not as great as in the previously discussed groups.

Diphtheritic infections in the ear were encountered in five patients, conjunctiva in three, skin in six, umbilicus in one and vagina in one, all representing primary disease except in three of the cutaneous cases. These and other extrarespiratory forms of the disease occur infrequently in this country. Usually they are neither diagnosed nor treated early and despite little or no systemic reaction may result in complications and death.

Cutaneous diphtheritic lesions may occur in one per cent of nasopharyngeal cases.[69] Lesions are usually multiple, variable in appearance and most frequently are situated on the extremities.[69,70] Preliminary application of sterile saline compresses will increase the per cent of positive cultures.[70] Livingood et al.[70] estimate that 90 per cent of cultures should be positive if taken in the first two weeks of the disease; the longer the delay in culturing cutaneous lesions, the greater the per cent of avirulent organisms found.[31,69] Complications, such as peripheral neuritis, have been reported in patients in whom avirulent organisms have been isolated from the cutaneous lesions.[31] Cutaneous diphtheria occurred in epidemic form in the tropics among combat troops during the hot rainy seasons under conditions of unpreventable poor personal hygiene.[70] Burns, postsurgical wounds and traumatic abrasions or ulcers have been implicated.[96,101,116] Secondary diphtheritic infections of empyema and thoracotomy wounds are described by Brock.[18] Complications such as neuritis usually develop later with cutaneous than with either nasal or tonsillar diphtheria.[70] Neuritis has been reported in 20 to 43 per cent and myocarditis was estimated to occur in only 5 per cent of cutaneous cases.[19,40,70] Deaths, mostly single, are reported by several authors and reviews. In addition to diphtheria antitoxin, many authors believe penicillin used locally and parenterally to be of definite value.[19,31,70] The two fatalities with cutaneous diphtheria in our series were in patients with associated throat involvement.

Keller[62] quotes Drury's review of 196 cases of diphtheria involving the ear in 1925. Keller[62] and MacKenzie[74] both reported prompt response to antitoxin in such cases.

Beacham and Rice[11] describe the first reported case of uterine cervical diphtheria. In a review of the literature they mention 121 cases of vaginal involvement reported by 1932. Interestingly, both the youngest, a five month old infant with complicating myocarditis, and the oldest patient, aged fifty-five, died.

Morrison[79] and Hogan[53] give excellent descriptions of the three types of diphtheritic conjunctivitis: catarrhal, pseudomembranous and membranous.

Diphtheria involving various parts of the mouth, together with the relevant literature, is reported by Anderson[5] and Riddel.[93] The gums, lips and floor of the mouth and tongue have been, on rare occasions, the site of infection. In 1914 Reiche[5] recorded forty-nine patients with lip lesions among 7,314 cases of diphtheria in Hamburg. Hoyne[54] reports a one month old infant with a continuous diphtheritic membrane extending from the tonsil and posterior pharyngeal wall down the esophagus into the stomach and involving one-eighth of the stomach surface, and reviews thirty-four more cases with esophageal involvement. In a twenty-four year old female Fleming[37] reports the occurrence of diphtheritic membranes on the floor of the mouth, root of the tongue extending to the lower gum and also lining the sulcus between the gum and lower lip; the anus and perianal areas; and also in the sulcus between the labia majora and labia minora extending into the vagina and over the urethral orifice. This patient's seven day old infant also was treated for nasal diphtheria, with both patients recovering. Wolfsohn[116] reports a patient with peripheral neuritis and myocarditis secondary to diphtheritic cystitis and urethritis following prostatectomy.

COMPLICATIONS

Complications (Table VII) occurred in 289 patients, a 20.2 per cent incidence. Associated complications and conditions were one instance each of chronic laryngitis, glottic edema, epiglottic edema, laryngeal stenosis secondary to intubation, non-specific purpura, "toxic" dermatitis, erythema multiforme, adrenal hemorrhage, diaphragmatic paralysis, anuria secondary to sulfonamide therapy and cerebral anoxia with athetosis secondary to laryngeal obstruction; two instances of lung abscess and two of liver necrosis in patients with chronic alcoholism; three instances of fatty degeneration of the liver in chronic alcoholics; and the occurrence

in five patients of thrombophlebitis secondary to intravenous therapy.

Factors Influencing Complications. The number of days between the onset of disease and the administration of diphtheria antitoxin: Table VIII indicates that the longer treatment is delayed, the greater is the developed pneumonia the longer the delay in starting specific treatment, the greater the mortality. Paley and Truelove[86] report an appreciable increase in complications, especially polyneuritis, with delay in therapy. The necessity for tracheotomy during the first week of the

TABLE VII

DIPHTHERIA COMPLICATIONS—AGE, INCIDENCE AND MORTALITY RATES

Age (yr.)	Myocarditis		Bulbar Paralysis		Peripheral Paralysis		Laryngeal Cord Paralysis		Otitis Media		Broncho-pneumonia		Kidney Complications		Facial Paresis		Encephalitis	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
0–1	1	1	..	..	..	....	..	...	2	0	3	2	..	....	..	..	..	...
1–5	27	19	7	3	4	1	2	0	12	0	39	22	6	6	1	..	1	1
5–10	39	25	11	0	2	1	3	0	4	0	23	18	2	1	1	..	..	...
10–20	16	5	3	2	5	1	..	...	6	0	3	3	1	1	..	..	..	...
20–30	10	2	7	0	4	0	1	0	1	0	7	2	..	....	1	..	..	...
30–40	16	7	7	2	6	0	3	0	2	2	10	8	2	2	..	..	1	1
40–50	15	8	9	1	7	1	3	0	1	1	9	8	2	2	..	..	..	...
50 plus	12	4	6	1	4	0	2	1	..	....	7	6	1	1	..	..	..	...
Total	136	71	50	9	32	4	14	1	28	3	101	69	14	13	3	0	2	2
Mortality (%)	...	52.2	..	18	..	12.5	..	7.1	..	10.7	..	68.3	..	92.9	..	..	..	100

A—total number of patients
B—total number of deaths

TABLE VIII

INCIDENCE AND MORTALITY RATES OF DIPHTHERIA COMPLICATIONS IN RELATION TO NUMBER OF DAYS FROM ONSET OF ILLNESS TO ADMINISTRATION OF DIPHTHERIA ANTITOXIN

Days	Total No. Patients	Myocarditis				Bulbar Paralysis			Peripheral Paralysis			Pneumonia				Bull-neck				Tracheotomy			
		A	B	C	D	A	B	D	A	B	D	A	B	C	D	A	B	C	D	A	B	C	D
1	236	11	6	54.5	4.7	2	1	0.8	1	0	0.4	4	1	25.0	1.6	17	4	23.5	7.2	9	2	22.2	3.8
2	250	15	7	46.6	6.0	8	2	3.2	5	2	2.0	15	8	53.3	6.0	31	6	19.3	12.4	17	6	35.3	6.8
3	273	28	12	42.8	10.3	12	0	4.4	6	0	2.2	22	14	63.7	8.1	56	16	28.6	20.5	53	19	35.8	19.4
4	203	21	10	47.6	10.3	4	0	2.0	2	0	1.0	13	8	61.5	6.4	26	11	42.3	12.8	28	12	42.8	13.8
5	157	20	15	75.0	12.7	8	3	5.1	4	0	2.5	13	11	84.5	8.3	15	7	46.7	9.6	32	15	46.8	20.4
6	65	6	1	16.7	9.2	3	0	4.6	0	0	0	5	5	100.0	7.7	9	3	33.3	13.8	16	6	37.5	24.6
7	112	13	6	46.2	11.6	4	0	3.6	6	0	5.4	14	10	71.5	12.5	12	4	33.3	10.7	20	7	35.0	17.8
8	104	22	14	63.6	21.2	11	3	10.6	8	2	7.7	10	10	100.0	9.6	7	4	57.2	6.7	10	6	60.0	9.6

A—Number of patients
B—Number of deaths
C—% mortality rate
D—% incidence = (A/total no. pts.) × 100.

incidence of myocarditis and, to a lesser degree, of pneumonia and bulbar and peripheral paralysis. The mortality rate in patients developing myocarditis, however, remained approximately the same regardless of the day antitoxin first was administered; whereas in patients who eventually disease increased with each day's delay in receiving antitoxin.

Immunization (Table IX): Lower mortality and complication rates in immunized patients are reported by Grant,[50] Carter[22] and Ipsen.[58] Grant reports that paralysis occurs five times

and bull-neck diphtheria more than fifteen times as frequently in non-immunized patients as in those adequately immunized. Carter's study shows a 3 to 1 incidence of paralysis in non-immunized as compared to immunized patients; the percentage occurrence of carditis, however, was only slightly less in the immunized group.

TABLE IX
INCIDENCE OF COMPLICATIONS IN IMMUNIZED AND NONIMMUNIZED PATIENTS

	Nonimmunized Patients				Inadequately Immunized Patients				Adequately Immunized Patients			
	Total No.	No. Died	Mortality (%)	Patients in Goup (%)	Total No.	No. Died	Mortality (%)	Patients in Group %	Total No.	No. Died	Mortality (%)	Patients in Group (%)
Myocarditis	58	32	55.2	10.5	8	6	75.0	5.4	6	3	50.0	5.8
Bulbar paralysis	23	4	17.4	4.2	3	1	33.3	2.0	1	0	0	1.0
Peripheral paralysis	6	0	0	1.1	3	1	33.3	2.0	1	0	0	1.0
Pneumonia	43	25	58.2	7.8	7	7	100.0	4.8	3	1	33.3	2.9
Bull-neck diphtheria	73	25	34.3	13.2	23	4	17.4	15.6	9	2	22.2	8.7
Total no of patients	552	54	9.8	....	147	11	7.5	....	104	3	2.9	....
Total no. of patients with complications	139	..	....	25.2	37	..	.....	25.2	14	..	....	13.4

Total No.—803 (56% of 1,433)
History no immunization —68.8%
History inadequate immunization—18.3%
History adequate immunization —13.0%

Age: In our series the incidence of myocarditis and bulbar and peripheral paralysis increased appreciably only in patients over thirty years of age, a contributing factor undoubtedly being the longer delay in seeking therapy. Pneumonia occurred, however, most frequently in both the younger and older age groups.

Type of bacteria: Carter[22] reports the incidence of complications usually is greatest in gravis, less with intermedius and minimal with mitis infections, both in immunized and non-immunized patients.

Types of Complications. Myocarditis: Clinical or pathologic evidence of myocarditis was found in 136 patients, an incidence of 9.5 per cent. The majority of electrocardiographic studies in our series were performed only on clinical suspicion of the presence of this complication. Electrocardiographic changes or clinical evidence of myocarditis are reported by Burkhardt et al.[20] in 20 per cent of 140 patients with toxic diphtheria, Gendel[42] in 10 to 20 per cent of all cases, Gaskill and Korb[40] in 5 per cent of 140 cases of cutaneous diphtheria, Hoyne and Welford[55] in 10.6 per cent of 4,671 patients, Livingood et al.[70] in 2.7 per cent of 109 patients with cutaneous involvement, Brainerd and Bruyn[17] in 36.6 per cent of 273 cases and Bower et al.[15] in 10 per cent of 278 patients. In series with more extensive electrocardiographic studies abnormalities were demonstrated in 85 per cent of severe cases,[4] 84 per cent of one hundred severe cases[16] and 65.5 per cent of ninety-three patients.[16] The majority of abnormalities in the last named group were slight and transient.

Our mortality rate of 52.2 per cent compares with figures of 62 per cent of 496 cases[55] and 36 per cent of one hundred patients.[17] The lowest fatality rate in our series was in the ten to thirty year age group (26.9 per cent), contrasted with 67.2 per cent in patients less than ten years of age. Among twenty-two alcoholics with complicating myocarditis the mortality rate was 40.9 per cent.

The incidence of myocarditis increased both with increasing age and with delay in treatment. (Table VIII.) When this complication did occur, however, the likelihood of a fatal outcome was increased only slightly in patients with increasing

delay in the initial administration of diphtheria antitoxin.

The electrocardiographic studies in seventy of the above patients are shown in Table x. There were three deaths among forty-four patients with only T wave changes, in contrast to the appreciably greater mortality rate in patients with conduction changes. There are many reports on the better prognosis in patients with T wave as compared with conduction changes.[8,16,20,63,73,83] Serial electrocardiographic and pathologic changes are well described by several authors.[20,26,73] Among our nine patients with complete heart block the slowest recorded ventricular rate was 18/minute in a twenty year old male who survived. Three other patients, all of whom died, had ventricular rates between 20 and 25. Goldstein and Calcagno[48] report a bradycardia of 10 or 11/minute in a thirty-three year old male patient who died on the tenth day. One of our patients with complete heart block survived for twelve months after the onset of illness, with demonstrable electrocardiographic changes until her sudden demise.[51] Leys[68] describes a patient with persistent electrocardiographic evidence of complete heart block fifteen years after occurrence of diphtheritic myocarditis. Reviews and case reports[3,35,68,77,81] reveal the relative rarity of survival in these patients. Engle[35] recently was able to find only twenty-seven such recoveries in the literature in addition to six more she reported from the Sydenham Hospital. The even rarer occurrence of subacute bacterial endocarditis due to C. diphtheria has been recently reported, with only rare survival recorded.[2,117]

TABLE X
ELECTROCARDIOGRAPHIC CHANGES IN SEVENTY PATIENTS WITH DIPHTHERITIC MYOCARDITIS

	Total No. Patients	No. Deaths
T-wave changes	61	9
Right bundle branch block	2	2
Left bundle branch block	6	2
First degree A.V. block	7	2
Second degree A.V. block	1	0
Complete heart block	9	7
Auricular fibrillation	1	1
Auricular flutter	1	0
Nodal rhythm	6	2
Wandering pacemaker	3	0
I.V. conduction defect	6	0

Three patients with ventricular tachycardia, two with gallop rhythm and five with a clinical diagnosis of peripheral vascular collapse all died. Death in the latter five patients occurred relatively early in the disease, in contrast to the fatal cases with conduction defects. Forty-two of the seventy-one deaths occurred within the first ten days after onset of the disease, compared to Hoyne and Welford's report of 79 per cent of myocardial deaths occurring within the first two weeks of illness.

The principles for treatment of this complication are based on the original work of Gordon and Hoyne and have been essentially unchanged in this hospital since our last report.[15,107]

Neuritis: The occurrence of neuritis in seventy patients in our series (forty-seven males and twenty-three females) would doubtless be greater were adequate follow-ups obtainable. These patients had the following involvement:

Pharyngeal	27
Peripheral	11
Laryngeal	3
Facial	3
Pharyngeal-peripheral	15
Pharyngeal-peripheral-laryngeal	4
Pharyngeal-laryngeal	5
Peripheral-laryngeal	1
Pharyngeal-laryngeal-diaphragmatic	1

Forty-three were over fifteen years of age and thirty-three over thirty years. This increased frequency of central nervous system complications in older patients is described by Ammundsen.[4] Death in three patients could be directly attributed to pharyngeal paralysis with secondary aspiration pneumonia. Pharyngeal paralysis usually occurred somewhat earlier than peripheral neuritis; in both types, however, the onset usually was slightly earlier in younger patients. Paralysis in 50 per cent of patients occurred thirty or more days following the onset. Though a lesser incidence than reported elsewhere,[20,73] the presence of concurrent neuritis and myocarditis in thirty-one patients indicates the necessity for continued close observation once either complication manifests itself. Pneumonia, frequently aspiration type, occurred in eleven patients, of whom six died.

The usual treatment prescribed for the case with nerve involvement, consisting of bed rest, a high polyvitamin intake, physiotherapy, and on rare occasion the use of the respirator, seems to

have little influence on the duration of the disease, with the vast majority of patients ultimately recovering normal function. Stolz,[104] however, advocates prostigmine as effective in accelerating healing of the neuritic process. Chemi's interesting observations[24,25] of progressive lowering of the blood phospholipids in postdiphtheritic neuritis led to the use of lecithin compounds intravenously, with a more favorable clinical course reported.

Encephalitis was demonstrated at autopsy in two patients. A one year old female, treated forty-eight hours after the onset of her illness, developed encephalitic symptoms on the twenty-eighth day and died two days later. At autopsy multiple petechiae, cerebral edema and microscopic changes consisting of generalized congestion of the smaller vessels with occasional extravasation of blood were present. The second patient was a thirty-seven year old female who died one day after entry. A left hemiplegia was present on admission. Two recent excellent reviews and several case reports indicate the rarity of encephalitis as a complication.[7,32,66] Hemiplegia is probably the most common form of diphtheritic cerebral involvement, usually being due to embolism secondary to cardiac thrombi. As seen in our first case, multiple small hemorrhages with cerebral edema are considered by many to offer sufficient pathologic evidence for the diagnosis of acute encephalitis.[32]

Pneumonia: This complication occurred in 101 patients, approximately two-thirds of whom had laryngeal or tracheobronchial involvement. Twenty-four and four-tenths per cent of all patients with diphtheria of the lower respiratory tract developed pneumonia, in contrast to 2.9 per cent with no such involvement. The death rate in patients with laryngeal or tracheal disease complicated by pneumonia also was appreciably greater than in the pneumonia patients with no lower respiratory tract involvement (78 and 50 per cent, respectively). The relative incidence of pneumonia in all cases was greatest before five and after thirty years of age. However, in patients with both lower respiratory tract diphtheria and pneumonia the incidence and the mortality were lowest in the younger age group, with both increasing appreciably with increasing age, especially over thirty. Among thirty-seven patients dying within five days 57 per cent had pneumonia, in contrast to 36 per cent of fifty-eight patients dying in the period five to ten days after the onset. The incidence of pneumonia was 50 per cent in our 137 fatal cases. Gore[49] reported this complication in 50 per cent of patients who died in the first five days and in 61 per cent of 221 fatal cases. In malignant diphtheria Kredba[65] found bronchopneumonia in 50 per cent of infants who died, in 30 per cent of older children and adults dying in the first two weeks and in 5 per cent of those who died at a later time. Incidentally, the response to penicillin was found to be poorer in early than in late pneumonias.[65]

Serum Reactions: This complication following therapy occurred in 126 patients (8.8 per cent). Immediate reactions due either to the test dose or to the full dose of antitoxin occurred in eight patients, all of whom recovered. Febrile reactions, most frequently occurring within twenty-four hours, were observed in fifty-eight patients, the majority being less than ten years old. Serum sickness occurred in fifty-nine patients, appearing between the second and eighteenth days following administration of antitoxin, most frequently between the sixth and ninth days. In contrast to the febrile reactions over 70 per cent of the patients with serum sickness were over ten years of age, and the majority of these younger patients has this complication later than the adults.

Miscellaneous Complications: Otitis media, present in twenty-eight patients most of whom were children, responded well to sulfonamide or penicillin therapy. Renal involvement, diagnosed either clinically or at autopsy, was observed in fourteen patients, only one surviving.

LABORATORY FINDINGS

Aside from bacteriologic investigations of the various types of diphtheria bacilli, there are relatively few reports in the literature concerning the various laboratory findings in diphtheria. Several recent articles, mainly in foreign literature, report culturing diphtheria bacilli in other than local lesions. Paschlau[88] and Wildführ[114] believe that the disease starts as a general infection with bacillemia, followed by a localized inflammatory reaction, most frequently seen in the tonsillopharyngeal area. In thirty-one patients with known exposure who developed the disease Wildführ obtained positive blood cultures in twenty-eight, a maximum incidence of positive cultures occurring two days before the onset of local symptoms in the throat. Bacillemia usually disappeared with localization of the disease.

Paschlau found positive cultures for diphtheria in the blood of 7.1 per cent of 405 cases, in the urine of 28 per cent of 361 cases, and in various organs at autopsy in 72 per cent of 190 cases. Arnold[6] reports obtaining positive cultures in varying percentage from ten different organs in forty-seven autopsied cases, the greatest incidence occurring in the lungs (40 per cent), cervical glands (33 per cent) and myocardium (30 per cent). He states that positive cultures were more numerous in patients dying in the acute stage of the disease, although he reports finding the organism in the myocardium of one patient who died six weeks after onset. Others report finding the organism in the blood[64,114,115,117] and other organs,[4] mostly in more severe and malignant forms of diphtheria.

Blood antitoxin level studies reported by Ipsen[58] and Gibbard et al.[43] indicate that a level of antitoxin capable of producing a negative Shick test is not an absolute guarantee of immunity against diphtheria. Instances of severe disease with antitoxin levels over $\frac{1}{100}$ unit at the onset of illness and two deaths in patients with titers of more than 1.0 unit per ml. are reported by the first named author. Ipsen found a distinct correlation between the course of the disease and the antitoxin content in immunized patients, but only minimal correlation in non-immunized individuals. He also states that in immunized and non-immunized patients with the same titer and clinical picture at the onset of the disease the course in the immunized group was milder and the rise in antitoxin titer more rapid and greater. Wildführ's[112] findings of seasonal variations in antitoxin titers were mentioned previously.

Albuminuria is more likely to occur in the more severely ill[48,55] and also in non-immunized patients.[50] Hoyne and Welford[55] also found albuminuria frequently preceding the onset of myocarditis.

Among the few reports on blood chemical changes are the findings of elevated blood urea levels, as well as temporary thrombocytopenia;[4] decreased phospholipids, especially with development of postdiphtheritic paralysis;[24,25] and increased serum globulin in moderately or severely ill patients.[47] Hoyne and Welford's blood sugar studies in twenty-nine patients with severe diphtheritic myocarditis revealed normal fasting blood sugar levels in eighteen and values above 120 mg. per cent in eleven patients. These authors, as well as Salmi and Lato,[97] found a slow fall in the blood sugar curve. Among disturbances in fatal cases reported by the latter authors were decreased albumin content and A/G ratio, positive flocculation reactions, decreased blood cholesterol, increased bilirubinemia and urobilinuria, and a pathologic blood sugar curve (rapid rise and slow fall). In a study of thirty autopsied cases Prosperi[90] found histologic changes in the adrenals corresponding to those responsible for experimental hypoglycemia in guinea pigs.

TABLE XI
WHITE BLOOD COUNT IN 1,353 DIPHTHERIA CASES

Total WBC	Total No. Patients	% of Total (1,353)	No. Deaths	Mortality (%)
<5,000	5	0.4	0	0
5,000–10,000	269	19.9	8	2.9
10,000–12,500	265	19.6	14	5.3
12,500–15,000	220	16.2	27	12.3
15,000–17,500	192	14.2	12	6.3
17,500–20,000	143	10.6	15	10.5
20,000–22,500	93	6.9	3	3.2
22,500–25,000	59	4.4	7	11.9
25,000–27,500	39	2.9	9	23.0
27,500–30,000	19	1.4	4	21.0
30,000–35,000	29	2.0	8	27.6
>35,000	20	1.5	9	45.0
	1353			

Mortality Rates: 0–10,000—2.9%
10–15,000—8.5%
15–20,000—8.1%
20–25,000—6.6%
25–30,000—22.4%
30,000 plus—34.7%

The spinal fluid in patients with postdiphtheritic neuritis usually shows an albuminocytologic dissociation.[17,30,40,59] According to Gaskill and Korb[40] the cell count is never increased. The protein content increases early and persists throughout the duration of neuritis, gradually returning to normal; this protein elevation may persist as long as three or four months after the onset of the illness.[32] Several reports[40,59,98] indicate that the degree of protein elevation usually is directly proportional to the severity of symptoms. In our series spinal fluid examinations revealed the usual protein increase with normal cell counts.

The white blood cell picture in the peripheral blood was studied in one hundred cases by

Baumgartner.[10] He found the number of mature neutrophils to be inversely correlated with the severity of the disease, decreasing in number with increasing severity. Mixed infections usually had higher white blood counts. Fisher and Cobb[36] found an average count of 20,600 with no direct correlation between severity of the disease and height of the white blood count. Table XI shows the relative incidence of the initial white blood count in 1,353 patients of our series, with the corresponding mortality rates in each group. The marked increase in fatalities in patients with counts over 25,000 is apparent. An appreciable number of the latter group had mixed infections, as demonstrated by throat cultures, and also had a higher incidence of complications. The approximate median white blood count on entry in 833 primary faucial cases was 13,000; in 96 nasal-faucial cases, 13,750; in 130 faucial-laryngeal cases, 16,500; in 152 bull-neck patients, 17,250; and in 71 patients with pneumonia, 19,000. These figures indicate the occurrence of a higher count in association with increasing spread and severity of the disease. The highest mortality in the pneumonia group, however, occurred in patients whose initial white blood counts were less than 15,000.

TREATMENT

Therapy in this hospital, both specific and general, has been essentially the same as previously reported.[15,107] The dose of diphtheria antitoxin varies from 20 to 80 thousand units, the amount and method of administration being determined by the extent of the diphtheritic process, duration of illness and apparent degree of toxicity.

Intubation was performed in only two patients. It has been replaced by tracheotomy in patients with laryngeal or tracheobronchial obstruction, and those with marked bull-neck involvement. The necessity for this procedure was slightly greater in younger than in older patients. Of 193 patients who were tracheotomized seventy-seven died, a 39.9 per cent mortality rate. Among 134 cases with bull-neck involvement fifty-one tracheotomies were performed with a fatality rate in this group of 37.3 per cent. Among 232 laryngeal patients 110 were tracheotomized, with 34 dying (30.9 per cent). Twenty-nine of thirty-nine patients with both laryngeal and bull-neck involvement required artificial airways. The mortality rate in these twenty-nine patients was 82.7 per cent. Complications secondary to this procedure occurred in twenty-one patients. Local wound infections were present in three patients, mediastinitis in one, tissue emphysema in sixteen, pneumothorax in five (four patients had right pneumothorax), and mediastinal emphysema in three.

In addition to diphtheria antitoxin, penicillin was given to approximately half the patients, no appreciable clinical difference being noted between patients who received it and those who did not.

Some recent interesting innovations in therapy are discussed in the current literature. Wannagat[110] treated 150 cases of toxic diphtheria with Buerger's method of peri- and retrotonsillar injections of antitoxin, with the theoretic objective of blocking the spread of toxin. Later, he modified the method by injecting 4,000 to 30,000 units of antitoxin daily into the jugular and subclavian areas and reported only two deaths in 181 cases. Sole[100] gave intravenous injections of 10 ml. of 10 per cent sodium thiosulfate to fifty severely toxic cases, with a low death rate of 12 per cent. Losche[72] claims to have reduced the mortality rate in very severe cases of diphtheria, all with electrocardiograms and clinical evidence of various severe cardiac complications (such as A-V block, Wilson block, etc.), from 65 to 16 per cent by the daily intravenous use of three to four ampules of co-carboxylase, an enzyme sold under the trade name berolase,® combined with 5 to 10 ml. of 20 per cent levulose solution.

SUMMARY

1. An analysis of 1,433 cases of diphtheria, observed during the ten-year period ending June, 1950, is reported.

2. The incidence, mortality rates and factors influencing complications are discussed.

3. The incidence in males was 54 per cent. The incidence in patients less than ten years of age was 57.7 per cent.

4. The mortality rate in this series was 9.6 per cent. Higher mortality rates were noted in patients less than five and over thirty years of age; in males as contrasted to females (11.6 and 7.2 per cent, respectively), and especially in the older age group; in patients with increasing delay in therapy; in chronic alcoholics (29.3 per cent in fifty-eight patients); and in patients with more extensive organic involvement.

5. Therapy, including newer innovations described in the literature, is discussed.

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Influence of Antibiotics on Immunologic Responses in Scrub Typhus*

JOSEPH E. SMADEL, M.D.
Washington, D. C.

I AM indeed grateful for the privilege of paying homage to the accomplishments and memory of Howard Taylor Ricketts in this, the fifth of the lectures which bear his name. Like my predecessors,[1–4] I shall follow the mandate of Dr. Wilder[1] and discuss certain aspects of the investigations with which I have been associated.

Since 1947 we have witnessed the therapeutic conquest of the important rickettsial diseases of man. The story of this successful campaign is a fascinating one which has been reviewed elsewhere and the resultant therapeutic regimens are now included in current textbooks. Therefore, rather than repeat at this time the basic theme of the broad spectrum antibiotics in the treatment of rickettsial disease, I wish to introduce a second theme, namely, the immunologic response in rickettsial infections, and to develop the composition along the line of interplay between the two.

Most of the work which I shall discuss was done in Malaya by investigators from the Army Medical Service Graduate School, working in collaboration with members of the Staff of the Institute for Medical Research in Kuala Lumpur. Most of the pertinent data were collected from volunteers who contracted scrub typhus during the course of the investigations. I cannot speak too enthusiastically about the esprit de corps of the scientists and the cooperation and tolerance of the volunteers. Since the volunteers assumed such an important role in the studies, I believe it worthwhile to digress for a moment to quote from the scientific report[5] of the experiment in 1948 in which volunteers were first employed in investigations on scrub typhus:

"Accordingly, when the results of studies on patients with tsutsugamushi disease indicated that this once dread infection could be reduced to a nonfatal illness in which the fever terminated, on the average, in 30 hours after chloromycetin treatment was begun, it seemed appropriate to proceed to test the chemoprophylactic value of this drug in men exposed to scrub typhus under natural conditions. . . .

"The original group of volunteers consisted of a number of investigators and assistants engaged in the study of scrub typhus at the Institute for Medical Research, Kuala Lumpur. Since it was possible that most of these possessed partial resistance to Rickettsia tsutsugamushi because of their occupational contact with the agent in the laboratory or in the field, or because of vaccination, it was deemed advisable to enlist additional volunteers. An official release by the Government of The Federation of Malaya announced the proposed test on the control of scrub typhus." This announcement successfully served its purpose, yielding approximately seventy applicants. Volunteers for subsequent studies were obtained in a similar fashion by announcements in the newspaper and over the radio. A total of several hundred participated during the period from 1948 to 1951. None ever became seriously ill and many returned time after time to take part in succeeding investigations.

IMMUNIZATION BY A COMBINED LIVING VACCINE-CHEMOPROPHYLAXIS PROCEDURE

The results of this first field test with volunteers exposed in endemic scrub typhus areas while receiving chloramphenicol as a chemoprophylactic agent are shown in Figure 1 which is reproduced from an earlier report.[5] The trial was extremely disappointing as regards the immediate hope for obtaining a successful chemoprophylactic measure for scrub typhus. The volunteers receiving antibiotic remained well during the period of prophylaxis but they developed scrub typhus about a week after the last dose of drug. Despite the failure as regards

* From the Department of Virus and Rickettsial Diseases, Army Medical Service Graduate School, Washington, D. C.
† Ricketts Award Lecture, presented at the University of Chicago, May 11, 1953.

its primary objective, the study illustrates several points which are substantiated by other observations. These points are: (1) the antibiotic which proved so valuable in treating patients with scrub typhus and which suppressed disease for a time in the volunteers failed to destroy the R. tsutsugamushi introduced by the infected mites; (2) even though the organisms remained viable under this type of chemoprophylactic regimen, they failed to induce immunity in the host and (3) continued contact of the agent with the antibiotic did not render it resistant, since the disease which subsequently developed was readily controlled by ordinary therapeutic amounts of chloramphenicol.

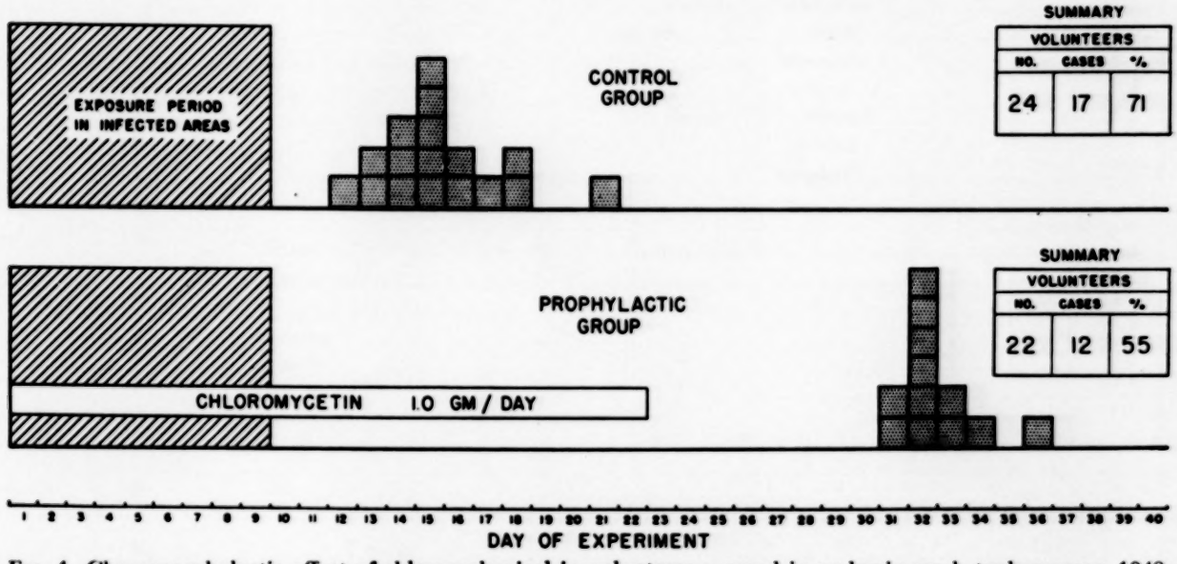
EXPOSURE PERIOD IN INFECTED AREAS
CONTROL GROUP
SUMMARY
VOLUNTEERS
NO. CASES %
24 17 71
PROPHYLACTIC GROUP
CHLOROMYCETIN 1.0 GM / DAY
SUMMARY
VOLUNTEERS
NO. CASES %
22 12 55
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
DAY OF EXPERIMENT

FIG. 1. Chemoprophylactic effect of chloramphenicol in volunteers exposed in endemic scrub typhus areas, 1948. (Reproduced from *Am. J. Hyg.*[5])

Additional information on chemoprophylaxis and the immunologic response was gained during a number of subsequent trails but only the last and most illuminating of these need be mentioned. Figure 2, which is reproduced from another report by our group,[6] summarizes the findings in volunteers who were vaccinated intradermally with living R. tsutsugamushi and given chemoprophylaxis by one of several schedules. Groups AA2 and BB3 provide an interesting contrast. The latter received six oral doses of 3 gm. amounts of antibiotic given at four-day intervals from the seventh to the twenty-seventh day after vaccination. All members of the group remained afebrile throughout the period of prophylaxis and subsequently. It is to be noted that five of the six volunteers had demonstrable rickettsemia during the period and that four of them developed a moderate but definite increase in OX-K agglutinins. Moreover, the four members who were tested for immunity one month later were found resistant to approximately one hundred infectious doses of either the Gilliam or Karp strains of R. tsutsugamushi. Thus this was a satisfactory living vaccine-chemoprophylactic procedure.

Volunteers in group AA2 received daily 1 gm. doses of chloramphenicol throughout the twenty-eight days following vaccination with sixty infectious doses of the Karp strain. The findings in this group differed significantly in several ways from those in group BB3. A cutaneous lesion did not develop at the site of vaccination in these volunteers whereas a primary lesion was characteristic of the response in members of the control and the other test groups. Rickettsemia was not demonstrable in repeated tests performed throughout the course of prophylaxis. And, most important of all, four of the six volunteers developed typical scrub typhus, requiring treatment, about a week after chemoprophylaxis was stopped and a fifth became ill at a later date. Despite the failure of this schedule there were some indications that an immunologic response was under way in this group, and it is possible that prolongation of the course of prophylaxis for another week or so might have resulted in protection such as obtained in group BB3.

The suggestion that the patients were re-

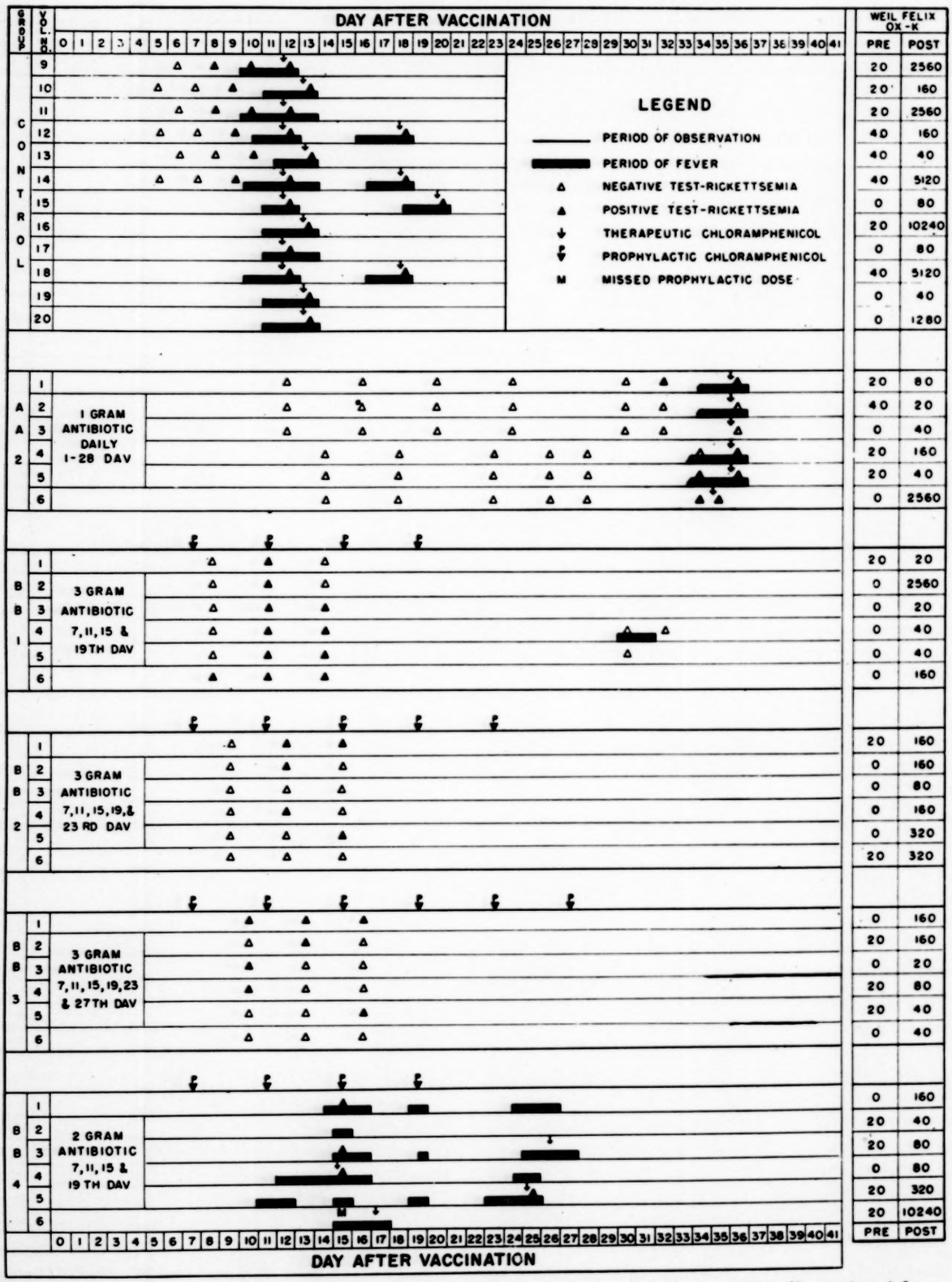

FIG. 2. Observations on individual volunteers in Karp vaccine-chemoprophylaxis test, 1951. (Reproduced from *Am. J. Hyg.*[6])

sponding immunologically to the rickettsiae, which probably were multiplying at a slow rate during the period of daily small doses of drug, were as follows: (1) only five of the six developed full-blown scrub typhus after prophylaxis was discontinued in contrast to a 100 per cent infection rate among the twelve volunteers in the control group; (2) none of the members of the AA2 group suffered a relapse after treatment (the significance of this will be discussed later) and (3) two of the six already had shown a four-fold increase in OX-K agglutinins several days before they broke through with clinical disease.

Groups BB1 and BB4 in the field trial under discussion also present interesting contrasts. The antibiotic was given prophylactically to both groups at four-day intervals from the seventh to the nineteenth day after vaccination. In BB1 the dose was 3 gm. while in BB4 it was 2 gm. The smaller dose was inadequate to suppress clinical disease since all six members of the group developed scrub typhus about the end of the second week. On the other hand, the schedule which employed 3 gm. doses up to the nineteenth day was almost adequate since it suppressed obvious disease during its course and only one of the six volunteers subsequently came down with scrub typhus. Group BB2 received a chemoprophylactic course intermediate between that of BB1 which was almost successful and BB3 which was entirely satisfactory. The results here are essentially comparable to those obtained with the longer course given group BB3.

The study which I have just described is one of a series which has introduced a new method for the controlled immunization of man against infectious agents. Setting aside for a moment the normal methods for acquiring immunity, i.e., suffering a classical attack of the disease, or of a mild but unrecognized form of the disease, or an entirely inapparent infection, one is left with the standard methods for inducing active immunity by inoculation of attenuated living strains of the agent or of non-infectious preparations of the agent. The present procedure consists of vaccinating with a strain virulent for man and subsequently controlling the extent of the infection by means of a chemoprophylactic agent. It is apparent from the data presented that satisfactory control of the evil genie, once introduced, is a difficult matter. Proper balance must be obtained in order to permit sufficient multiplication of the agent to provide an adequate immunologic stimulus. If the balance is tipped one way, so much suppression of the organism is obtained that an inadequate antigenic mass of rickettsiae is formed, with the result that immunity is delayed or does not appear. If tipped the other way, i.e., toward inadequate suppression, the volunteer develops full-blown disease. It is hardly necessary to point out that a procedure which is so difficult to adjust has very definite limitations in the immunization of man. However, one should keep in mind that scrub typhus is only one of several acute infectious diseases in which ordinary vaccination procedures are unsatisfactory and the new method may have some restricted application in these. I should point out that while the use of this type of suppressed infection as an immunizing procedure is new in human medicine, it had been used earlier in veterinary medicine. Alexander and his colleagues[7] at Onderstepoort, in the Union of South Africa, as early as 1941 employed a similar procedure for immunizing cattle against heart-water fever. In this instance non-immune animals were inoculated with blood from an infected bovine and subsequently were given prophylactic doses of a sulfonamide at a proper stage in the incubation period. We were ignorant of the South African work at the time of our Malayan studies; the learning of it emphasized to us once more the many contributions which veterinary medicine has made to human medicine and the need for greater awareness of this by physicians.

RELAPSES IN TREATED PATIENTS

A little earlier I mentioned relapses in patients who were treated with antibiotics. This interesting phenomenon in scrub typhus was limited almost entirely to our volunteers. Furthermore, as information accumulated, it became predictable and preventable by administration of a single supplementary 3.0 gm. dose of antibiotic at the appropriate time. Figure 3 summarizes certain information on the conditions under which relapses occurred. It was employed in a presentation at the annual meeting of the American Association of Immunologists in 1952[8] but is based on data reported in earlier publications.[5,9–11] It represents the experience in the treatment of a large group of patients with scrub typhus, all of whom became infected under natural conditions. Those included in groups A, B and C were patients who contracted the disease during the normal course of their labors. Those in groups D and E were volunteers

who became infected as a result of sitting in the grass in endemic scrub typhus areas in the vicinity of Kuala Lumpur.

The nineteen patients who made up group A in Figure 3 received only supportive treatment since specific antibiotic therapy was not available at the time. It may be noted that the febrile disease extended well into the third week after onset. On the average, the patients suffered 17.1 days of fever but one was febrile for thirty-one days. None of these patients relapsed. The thirteen patients in group B were treated with para-aminobenzoic acid over a period of five and a fraction days. The patients in group C were treated over a period of about thirty hours with one of the broad spectrum antibiotics. The majority received chloramphenicol or aureomycin but a few were given terramycin. These responded rapidly and here again relapses were not encountered. It may be noted that, on the average, therapy in the forty-nine persons in group C was begun on the seventh day of disease and ended on the eighth.

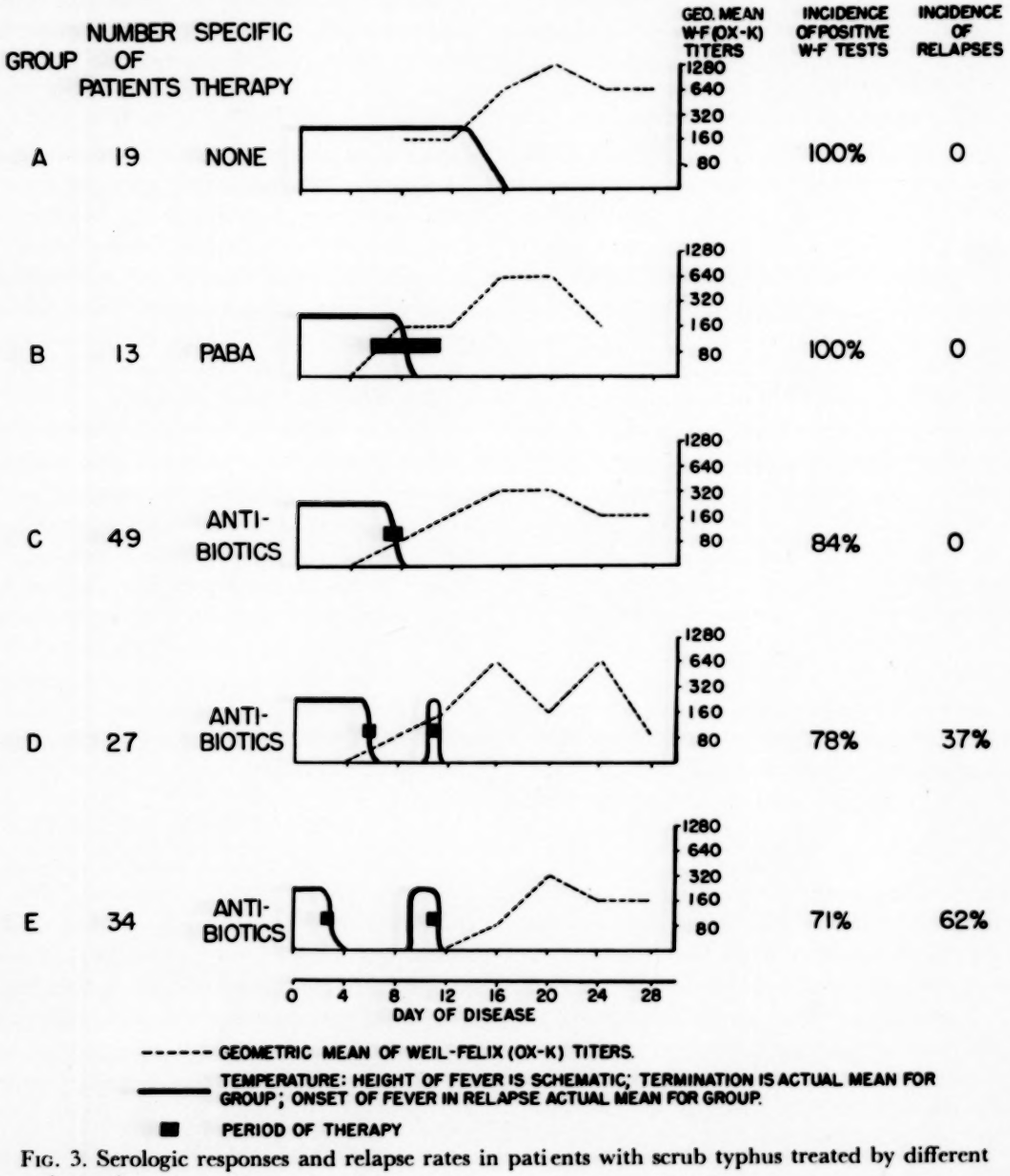
GROUP
NUMBER OF PATIENTS
SPECIFIC THERAPY
GEO. MEAN W-F (OX-K) TITERS
INCIDENCE OF POSITIVE W-F TESTS
INCIDENCE OF RELAPSES
A 19 NONE 100% 0
B 13 PABA 100% 0
C 49 ANTI-BIOTICS 84% 0
D 27 ANTI-BIOTICS 78% 37%
E 34 ANTI-BIOTICS 71% 62%
1280
640
320
160
80
0 4 8 12 16 20 24 28
DAY OF DISEASE
GEOMETRIC MEAN OF WEIL-FELIX (OX-K) TITERS.
TEMPERATURE: HEIGHT OF FEVER IS SCHEMATIC; TERMINATION IS ACTUAL MEAN FOR GROUP; ONSET OF FEVER IN RELAPSE ACTUAL MEAN FOR GROUP.
PERIOD OF THERAPY

FIG. 3. Serologic responses and relapse rates in patients with scrub typhus treated by different regimens.[8]

The volunteers who made up groups D and E were treated with either aureomycin or chloramphenicol and approximately one-half of them suffered relapses which were characterized by a return of fever and other signs and symptoms of

the disease, and by reappearance of rickettsemia. The sixty-one patients in this group were divided on the basis of whether they were treated before or after the fourth day. On the average, those in group D were treated on the sixth day and those in group E on the third day after onset. In both groups, about five days after therapy was stopped the patients began to relapse. The incidence of relapses was unrelated to the antibiotic employed but appeared to be affected by the time at which the drug was given. Thus 37 per cent of those treated on the sixth day suffered a recrudescence while 62 per cent of those treated on the third day had a recurrence of disease. The difference in rates between these two groups approaches statistical significance ($X^2 = 3.3$).

These and other findings have led us to formulate an hypothesis regarding relapses[11] which is based upon (1) the observation that the specific antibiotics are rickettsiostatic rather than rickettsiocidal, (2) the observations that a single large dose of antibiotic suppresses disease for five or six days and (3) the general experience that the untreated uncomplicated disease lasts on the average about fourteen days. We have assumed that the termination of the disease in the patient who receives only supportive treatment indicates the time at which the immunologic defenses of the patient have overcome the invading rickettsiae, and that for some unknown reason in the typhus fevers it takes about two weeks of illness before these defenses are completely mobilized. Thus practically all patients treated after the seventh day would have begun to develop appreciable immunity about the time the suppressive effect of the antibiotic was lost. On the other hand, few of those treated during the early days of illness would have been allowed an adequate interval for the immune mechanisms to become effective by the time the drug effect was dissipated. Hence the former group would be expected to have a low incidence of relapses and the latter a high incidence. There is no justification for concluding from the data presented that the antibiotic itself interferes directly with the development of immunity.

In this connection mention should be made of certain of the observations dealing with the occurrence of rickettsemia in patients with scrub typhus. It was rather consistently observed in volunteers that rickettsemia was detectable twelve to twenty-four hours before the onset of fever, headache and other constitutional signs of illness. Furthermore, rickettsemia continued for twelve to twenty-four hours after antibiotic therapy had effected clinical control of the disease and rendered the patient afebrile. Finally, volunteers on intermittent chemoprophylactic regimens which were adequate to suppress clinical signs of disease frequently had demonstrable rickettsiae in their blood. These facts were learned during the course of several years but each of them is illustrated in Figure 2. This pattern of infection with circulating pathogenic micro-organisms but without obvious clinical disease is probably not unique for scrub typhus. However, such a pattern is quite different from that which one usually regards as typical in the bacterial diseases. Such findings in scrub typhus lead one to speculate as to why the patient shows clinical manifestations at one stage in the rickettsemia but not at another. I know of no explanation but wonder whether clinical disease becomes manifest only when multiplication of rickettsia reaches or exceeds a certain critical level. Presumably, such a level would be one which yielded an appreciable amount of toxic products from host cells undergoing destruction, as well as from the rickettsiae themselves. At any rate, such observations on rickettsemia without fever may help to explain the prolonged clinical suppression of disease, i.e., for five or six days, obtained with a short course of specific antibiotic. The drug itself is dissipated within twenty-four to thirty-six hours after the last dose but one may assume that an appreciable period of time is required following elimination of the antibiotic before rickettsial growth again reaches a level sufficient to produce detectable rickettsemia, and that additional time is required for the rickettsemia to reach the hypothetic critical level associated with clinical disease.

SEROLOGIC REPONSE IN SCRUB TYPHUS INFECTIONS TREATED BY DIFFERENT REGIMENS

Definitive information regarding the effect of antibiotics on formation of antibodies in patients with bacterial diseases has become available in the last few years. In general, the results fall into two divergent categories, i.e., either appreciable suppression of antibodies or no effect on antibody formation.

One of the most comprehensive of these studies is that of Wannamaker and his colleagues.[12] These workers demonstrated, as had others before them, that prompt and adequate treatment of acute streptococcal respiratory infections with

penicillin materially inhibits the formation of antistreptolysin antibodies; moreover, they showed that the incidence of rheumatic fever was markedly reduced in the treated as compared with the untreated groups. In contrast, Jordan and his associates[13] observed no detectable alternation in serologic response as the result of penicillin treatment of cases of pneumococcal pneumonia and suggested that one of the important differences to be considered in these two contrasting types relates to the mass of antigenic material available for stimulating a response. We shall return to this thesis after examining the data on the OX-K response in patients with scrub typhus.

Information on the mean titer of agglutinins in the sera of scrub typhus patients at different periods during the course of illness is shown in Figure 3, and represents the response in a rather homogeneous group of patients infected by mites and treated according to different regimens. The patients in group A who received only supportive therapy were diagnosed on the basis of clinical findings and a positive Weil-Felix test. No serum specimens were available during the first week of illness but early in the second week titers of 1:160 were obtained and, starting about the twelfth day, there began a steady rise which reached a maximum of 1:1280 by the end of the third week. This antibody response in patients who suffered a febrile disease averaging seventeen days may be considered the usual response in respect to the Weil-Felix test in patients with scrub typhus who received no specific therapy.

The patients in group B, treated with para-aminobenzoic acid, displayed antibody responses resembling those in group A. These patients came under observation rather early in their illness and were first found to have developed detectable OX-K agglutinins on the eighth day. The mean titer rose, reaching a maximum of 1:640 during the third week. It may be noted that all of the patients developed a positive Weil-Felix test and that the difference in the mean maximal titers in groups A and B are within the limits of error of the serologic technic.

The patients in group C whose treatment with chloramphenicol, aureomycin and terramycin began, on the average, on the seventh day of disease also had detectable OX-K agglutinins early in the second week of the illness. While the titers rose, they reached a maximum of only 1:320 during the third week after onset. It should be pointed out that approximately one-sixth of the members of this group failed to show a positive Weil-Felix test, i.e., a fourfold increase in titer during convalescence or a single value of 1:160 or greater. The diagnosis of the patients who failed to develop a positive Weil-Felix test was established by isolation of rickettsiae during the acute illness. When appropriate statistical tests were applied, it was found that neither the mean maximal titer nor the incidence of positive reactions in group C was significantly different from those in groups A and B

The volunteers in group D whose treatment was begun on the sixth day displayed a serologic response which was quite similar to that in the preceding groups. OX-K agglutinins began to increase after the eighth day and reached a maximal titer of 1:640 on the sixteenth day. The serologic response of the volunteers in group E was appreciably different from that of the members of the other groups. There was a marked delay in the appearance of the OX-K agglutinins which first became detectable at a titer of 1:80 on the sixteenth day. However, during the next few days the titer rose, reaching a maximum of 1:320 on the twentieth day. Although only 71 per cent of this group developed a positive serologic response, this lower incidence is not significantly different statistically from that of groups A, B or C. To summarize briefly, the use of specific antibiotics in patients with naturally acquired mite-borne scrub typhus is without appreciable effect on the eventual height of the titer of OX-K antibodies. However, if therapy is begun quite early in the course of the disease the appearance of agglutinins may be somewhat delayed.

Additional information on the effect of antibiotics on the serologic response in scrub typhus infection is to be gained by a more detailed examination of the OX-K titers of the volunteers vaccinated with living Karp organisms in the test summarized in Figure 2. The mean titers according to day after vaccination are presented for several groups in this study in Figure 4. In the control group, whose members were treated within the first three days of onset of sustained fever, the mean titers remained below 1:40 during the first ten days after onset but reached 1:160 by the fifteenth day and 1:640 by the end of the third week. The majority of the members of groups BB1, 2 and 3 who received adequate intermittent suppressive chemoprophylaxis developed a fourfold increase in OX-K antibodies.

However, it is to be noted that during the fifth week after vaccination the level was 1:40 and by the seventh week had reached only 1:80. A response of a similar low order was observed in group AA2 who received continuous prophylaxis for a month. It will be recalled in passing that the first week of illness the levels approximate those in untreated patients who run the full course of two weeks of fever. These responses in scrub typhus would appear to depend upon the quantity of rickettsial antigen which becomes available for stimulating antibodies. The re-

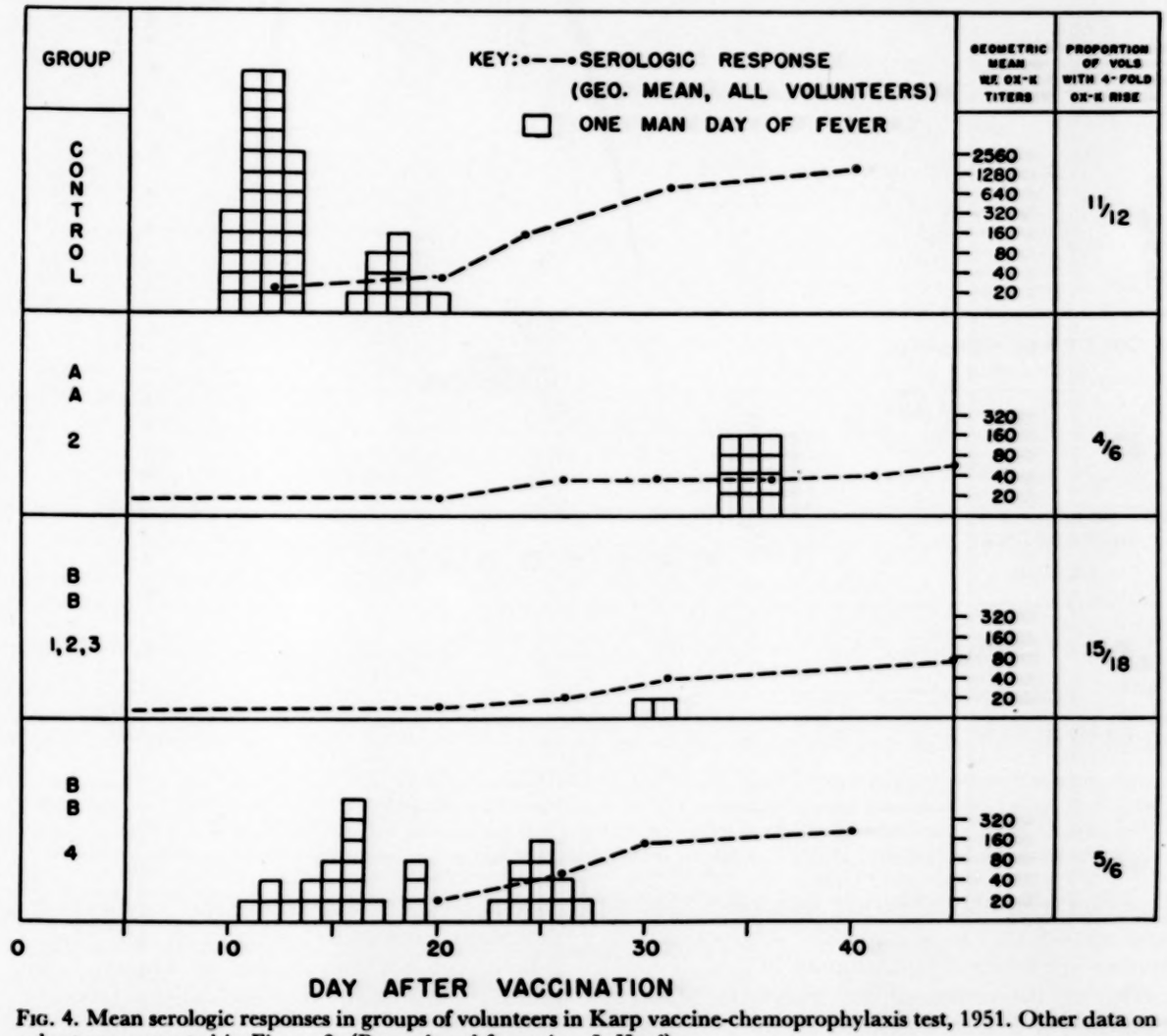

FIG. 4. Mean serologic responses in groups of volunteers in Karp vaccine-chemoprophylaxis test, 1951. Other data on volunteers presented in Figure 2. (Reproduced from *Am. J. Hyg.*[9])

group BB became immune while group AA did not; hence in these volunteers the low level of OX-K antibody has no relation to resistance.

Thus the serologic response in patients with scrub typhus infection, as measured by OX-K agglutinins, may be either unaffected by antibiotics or may be markedly depressed, depending on the course of treatment and the time it is instituted. If the drug is used prophylactically to obtain clinical suppression of disease, the antibody levels remain low. On the other hand, in patients who are treated after the latter part of sponses in this one disease, therefore, are analogous both to that of patients with streptococcal infections who are treated early and have depressed antibody formation and to that of pneumococcal pneumonia patients whose levels are unaffected by treatment.

RESISTANCE TO REINFECTION

The organisms which are classified as R. tsutsugamushi possesss marked differences in antigenic structure. These are detectable by means of complement-fixation, neutralization,

antitoxin and cross-vaccination tests and are assumed to account for the failure of inactivated vaccines to protect human beings in several field trials which have been undertaken; this phase of the problem is reviewed elsewhere.[14] Despite these antigenic variations, mice recovered from result of intradermal vaccination with a small dose of viable Gilliam organisms. Shortly following treatment and recovery he was again injected with Gilliam rickettsiae and remained well.

The results of a detailed examination of this phenomenon in volunteers who originally had

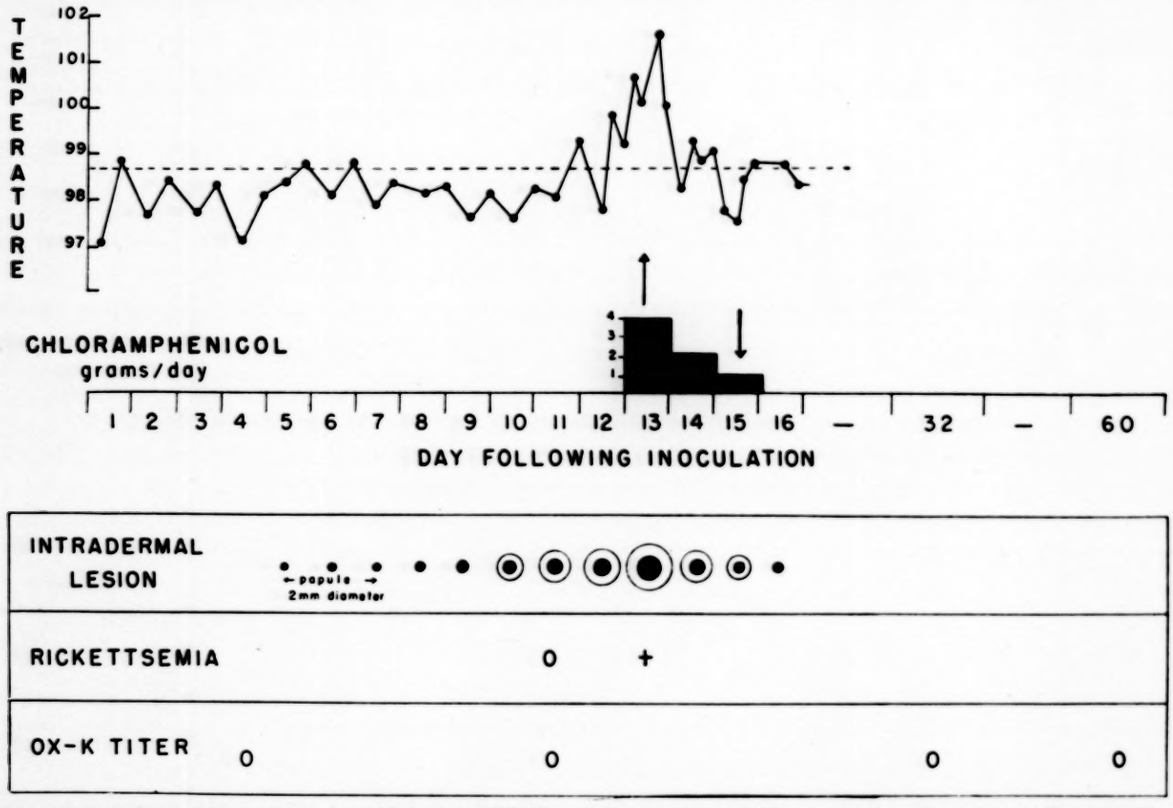

FIG. 5. Reinfection in scrub typhus. Volunteer CP-25 experienced his initial attack of scrub typhus in June, 1948. The clinical chart summarizes the findings following intradermal inoculation with 12 MID_{50} of the Gilliam strain of R. tsutsugamushi in January, 1950. This illustrates the transient nature of immunity in scrub typhus.

infection with one strain are resistant to others and second attacks of naturally acquired scrub typhus are relatively uncommon in man.

During the course of the studies in Malaya information was accumulated on the persistence of immunity in volunteers to homologous and heterologous strains of R. tsutsugamushi.[15,16]

Our first experience with the evanescent nature of immunity in this disease is illustrated in Figure 5. This volunteer, who had suffered scrub typhus from exposure in the field during the original chemoprophylactic trial in the summer of 1948, developed typical disease following intradermal inoculation of a few infectious doses of the Gilliam organism in January 1950.

This may be contrasted with the experience of Volunteer 608, whose record is summarized in Figure 6. This man developed scrub typhus as a participated in studies on the immunization procedure employing live vaccine and chemoprophylaxis are summarized in Figure 7. The tabular data show that volunteers recovered from suppressed or overt infection with Gilliam organisms were immune a year later when retested with the same strain (inoculum 1,000 mouse infectious doses). However, other similar volunteers developed scrub typhus when injected with the heterologous Karp strain (125 mouse infectious doses) either two months or fourteen months after recovery. The figure also shows that volunteers who experienced a suppressed infection with the Karp strain were resistant a month later to the homologous organism but some were susceptible to the Gilliam organism.

Observations made on other volunteers who contracted scrub typhus from mite bites during

field exposure and were subsequently tested for resistance to the Gilliam strain were, in general, comparable with the data summarized in Figure 7, as were the Japanese studies on men infected with the relatively mild Pescadores strain and rickettsial diseases of man (and I might add, parenthetically, that none of the other rickettsial agents possesses the antigenic heterogenicity of R. tsutsugamushi). Nevertheless, there are similarities in immunologic pattern between

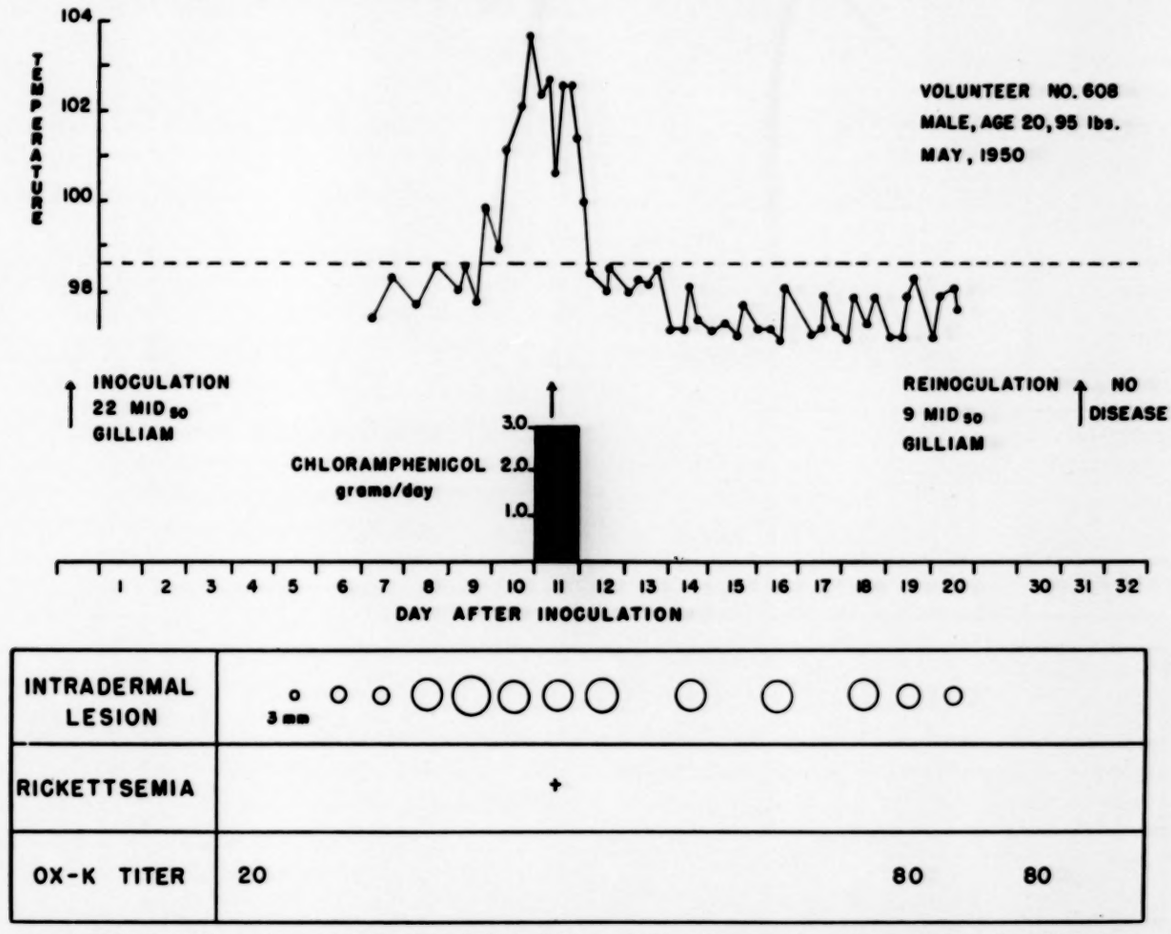

FIG. 6. This chart illustrates certain features of clinical disease induced by intradermal inoculation of small amounts of R. tsutsugamushi and the resistance of the recovered patient to the homologous organism. (Reproduced from *Arch. Path.*[15])

later inoculated with the more virulent Niigata strain.[17]

The important conclusions to be drawn from this phase of the work are (1) that resistance to reinfection with the homologous strain of R. tsutsugamushi persists at a high level for at least a year, and (2) that resistance to heterologous strains is of a transient nature and begins to disappear within a month or so. During the period of waning immunity the disease which results from a heterologous strain is mild but that occurring at one year presents the typical picture of scrub typhus.

These characteristics of immunity in scrub typhus have no known analogy among the other scrub typhus and certain of the viral and bacterial diseases. Sabin,[18] employing two immunologically distinct types of dengue virus, found volunteers solidly immune to the homologous type for at least eighteen months, and to the heterologous type for only several months. However, challenge with a heterologous strain resulted in modified disease at six months and typical disease at one year. The even more complicated nature of the problem of immunity in streptococcal infection is reviewed by Swift[19] who states, "Because antibacterial immunity to group A streptococci is closely connected with type specificity, it is understandable how one person might suffer many streptococcal infec-

tions, each due to a different type, for there are about forty recognizable types and probably many more as yet unrecognized."

PERSISTENCE OF R. TSUTSUGAMUSHI IN RECOVERED PATIENTS

A number of the rickettsial agents including R. tsutsugamushi have the property of remaining viable but dormant in the tissues of recovered infected animals. This state of mutual tolerance of the host and rickettsia has been termed "prémunition" by Parrot and Parrot.[20] Moreover, Zinsser[21] in developing his hypothesis regarding the cause of Brill's disease in immigrants stated, "This view implies the premise that the virus of typhus, once acquired, remains latent for many years in an indeterminable number of individuals and may become active in a fraction of these under circumstances of fading immunity." The role of R. prowazeki in Brill's disease has become increasingly evident in recent years[22] but isolation of the organism from healthy persons recovered from epidemic typhus remains to be accomplished.

VOLUNTEER HISTORY	CHALLENGE STRAIN			
	GILLIAM		KARP	
	NO. VOLS. TESTED	CLINICAL DISEASE	NO. VOLS. TESTED	CLINICAL DISEASE
SUPPRESSED GILLIAM 14 MO. PREVIOUS	6	0	5	5
TREATED GILLIAM 14 MO. PREVIOUS	6	1	5	5
NO PREVIOUS SCRUB	8	8	7	7
SUPPRESSED KARP 1 MO. PREVIOUS	8	3	8	0
TREATED GILLIAM 2 MO. PREVIOUS	—	—	4	4
NO. PREVIOUS SCRUB	3	3	3	3

FIG. 7. Summary of resistance of volunteers to reinfection with homologous and heterologous strains of R. tsutsugamushi. (Reproduced from *Am. J. Trop. Med. & Hyg.*[16])

The continued availability of a group of persons whose original scrub typhus infection had been carefully followed led us to attempt elucidation of the question of the persistence of rickettsiae in the tissues of apparently healthy recovered cases.[23] Twelve of the volunteers who had developed scrub typhus as a result of participation in chemoprophylactic field trials during 1948 and 1949 were persuaded to permit surgical removal of a palpable axillary or epitrochlear lymph node in 1950. Rather elaborate isolation procedures for R. tsutsugamushi were applied to the biopsy materials. Among the twelve persons who had had scrub typhus from one to two years previously, only one supplied a node from which R. tsutsugamushi were recovered. Eight of the volunteers were retested for resistance to 10 to 100 minimal infectious doses of the Gilliam organism. Four of these, including the volunteer whose node had yielded rickettsiae, remained well while the other four again suffered an attack of scrub typhus. It is of interest that only two of the eight had detectable scrub typhus complement-fixing antibodies prior to challenge; neither of these had demonstrable rickettsiae in his node removed for study but both were among those who resisted reinfection. Despite the absence of clinical manifestations in the resistant group, there was evidence of an immunologic response to the inoculum since complement-fixing antibodies appeared or increased in titer.

This demonstration of the persistence of R. tsutsugamushi in the tissues of recovered persons adds another factor to be reckoned with in any consideration of resistance to heterologous strains. The occasional individual who is immune to a presumed heterologous strain several years after initial infection may be one of those who retained his rickettsiae and frequently stimulated his immune mechanism. Even more important, the heterologous immunity which lasts for a few months after recovery may depend on the continued presence of a considerable number of organisms during this period. Kuwata[24] has recently shown that the apparent immunity of convalescent mice to a heterologous strain of R. tsutsugamushi represents a non-fatal, clinically inapparent superinfection with the second strain.

Additional evidence regarding the continued presence of rickettsiae in lymph nodes of recovered patients has been presented recently by Woodward and his colleagues.[25] They isolated R. rickettsii from a node removed from a man one year following an attack of Rocky Mountain spotted fever. A discussion of persistence of rickettsiae in man should mention the recovery of R. quintana in lice fed on patients long after an initial attack of trench fever [see references cited in (23)]. Since such successful isolations were almost always made during or

shortly after a recrudescence of disease, they resemble the experience of Murray and Snyder[22] in the recovery of R. prowazeki from patients with Brill's disease rather than the observations already mentioned concerning healthy persons who had remained well since their attack of scrub typhus or spotted fever.

CONCLUSIONS

In the forty odd years since Ricketts began making his major contributions to the infections which have come to be called "the rickettsial diseases," the agents, the vectors, the control measures and the specific treatments have been discovered. Truly, such knowledge represents potential conquest of the rickettsial diseases. The application of this available knowledge has, indeed, reduced the rickettsial diseases to a role of minor importance as regards the health and welfare of populations in many parts of the world, including the United States. However, as long as reservoirs of infection continue to exist in nature, or in populations in less fortunate areas, the rickettsial diseases will remain a threat to civilization. Therefore, I cannot view the situation with complete optimism. The present control and therapeutic measures demand the support of a vigilant, economically productive, highly industrialized society. If any one of these factors is lost through disinterest or through the destructions of war, the rickettsial plagues will again descend upon us.

Although this discussion has been concerned with an "exotic" disease which does not exist in the Western Hemisphere, a number of the points raised have actual or potential application to problems encountered in communicable diseases in the United States. For example, the idea that specific therapy should be administered on a continuous or intermittent basis only until the patient begins to develop his immune response to the infection appears to be as applicable in typhoid fever[26] as in scrub typhus, and doubtless in other acute infectious diseases as well. Furthermore, the observations on scrub typhus strengthen the concept that the serologic response of patients with infectious disease is heavily dependent upon the mass of antigen released in the body by the pathogen and that under certain special circumstances specific therapy may delay or diminish antibody production by interfering with the development of the usual mass of antigen. Immunization by means of a vaccination procedure employing chemotherapeutic control of infection induced by a virulent micro-organism might provide a protective measure against human pathogens other than R. tsutsugamushi which do not readily yield satisfactory vaccines of the attenuated living or non-infectious types. The persistence of virulent organisms in the clinically recovered patient is a more common phenomena than indicated by the few examples recorded in the rickettsial diseases. Besides, the classical example of tuberculosis, the typhoid carrier and the psittacosis carrier[27] come to mind. One wonders how often brucella lie dormant for long periods in the tissues of recovered patients ready to attack when the defenses of the host are temporarily lowered by poorly understood phenomena. Finally, the influence of antigenic complexity of closely related agents on immunity to other members of the microbial group, which is so clearly brought out in scrub typhus, is also recognizable in a number of viral and bacterial diseases.

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Seminars on Antihypertensive Drugs

Treatment of Hypertension*

S. W. HOOBLER, M.D.
Ann Arbor, Michigan

HYPERTENSION is a clinical manifestation rather than a disease entity. Of the more common clinically encountered causes of elevated blood pressure the following may be listed in approximate order of frequency:

1. Essential Hypertension. This is recognized by exclusion of other causes.

2. Hypertension Secondary to Arteriosclerosis. This somewhat ill defined entity should include most cases of primarily systolic hypertension in patients with obvious arteriosclerosis, and cases with onset after the age of fifty-five to sixty in which the elevation is principally in the systolic reading, as well as patients with diabetes or premature arteriosclerosis. Heart block and other causes for bradycardia may accentuate the systolic elevation. The diastolic blood pressure rarely exceeds 110 mm. Hg. These patients generally need mild symptomatic treatment only (salt restriction, Rauwolfia alkaloids) and carry a reasonably good life expectancy. In fact systolic elevations of blood pressure of approximately 100 plus the patient's age have been described as part of normal senescence.[1]

Patients who acquired essential hypertension and have survived into later years require differentiation since their prognosis may not be benign and they may respond to drug treatment cautiously used.[2] If historical information be lacking, a diastolic blood pressure usually exceeding 120 with or without major signs of cardiac or cerebral impairment may exclude the diagnosis of arteriosclerotic hypertension and call for therapy for established hypertension, although it is more cautiously applied in the elderly.

Hypertension secondary to unilateral renal disease may also occur de novo in the elderly. In Perera's series hypertension due to this cause had its onset after the age of fifty in 25 per cent.[3] Many of these were the result of unilateral vascular lesions of the renal artery. A recent experience of ours with two cases, one associated with fibrotic ureteral obstructions and another after neoplastic ureteral infiltration, suggests that malignant growths may also initiate the syndrome in the elderly.

3. Labile Blood Pressure. This classification is introduced to describe individuals whose systolic and/or diastolic pressures are occasionally elevated slightly but usually are normal. Their life expectancy is excellent and they need chiefly reassurance as treatment. They are usually discovered following routine examination for insurance or for army service. The older they are, the more benign the prognosis. In the younger person stress should be laid on the usually benign outcome. In a study of mortality from cardiovascular disease over a thirty-five-year period among twenty-five year old army officers exhibiting transient hypertension, an increase of only 3 per cent over the expected rate for non-hypertensive individuals was observed.[4] The fact of rejection and the frequent family history of hypertension tend to exaggerate the symptoms of vasomotor lability these persons often display. These episodes are sometimes fancied by the patient to represent impending angina and apoplexy, and may be further exaggerated by hyperventilation and magnified by a physician's careless words. Such patients need reassurance, the acquisition of new attitudes toward living and the counsel of a wise physician. Drug treatment is very rarely indicated as it destroys the value of reassurance. On the other hand, it is equally unwise to advise the patient "to forget the blood pressure," since from such individuals will come the bulk of patients with established or malignant hypertension. Therefore it is well to minimize the disease to the patient but to suggest regular annual re-evaluation.

4. Malignant Hypertension. This is defined as a high, fixed diastolic blood pressure accompanied by papilledema. Other definitions have

* From the Department of Internal Medicine, University of Michigan, Ann Arbor, Mich.

been proposed, none perfect, but this appears to be the most workable one and conforms closely to the original description.[5]

5. Hypertension Secondary to Bilateral Renal Disease. A history of renal disease with marked urinary abnormalities before or at the onset of pregnancy accompanied by more than usual weight gain and increasing albuminuria. It is important to distinguish this from pregnancy in a patient with essential hypertension, since this latter state is far too often considered *per se* to indicate the necessity for interruption. Great

TABLE I

RATIONALE FOR REDUCING BLOOD PRESSURE IN ESSENTIAL HYPERTENSION

	Acute	Chronic	Remarks
Theoretic Advantages:			
Reduction of cardiac work in hypertensive heart failure	Yes	Yes	Maintain blood pressure as low as possible[6]
Prevention of cerebral hemorrhage	No	?	Maintain blood pressure below 200 systolic; treatment of acute hemorrhage not very successful; prevention of hemorrhage unproved but likely
Prevention of atherosclerosis	No	?	Animal experiments plus absence of pulmonary vascular disease in hypertension support theory
Prevention of renal deterioration as in malignant exacerbation of essential hypertension	?	?	Objective is maximum reduction without inducing renal failure; diverse successful hypotensive therapy may stop progressive deterioration, rarely restores normal renal function[13]
Theoretic Disadvantages:			
Hypotensive accidents	Yes	Yes	Proportional to selection of cases and vigor of therapy
Dangerous side effects from treatment	Yes	Yes	Sympathectomy—mortality 2 to 10%. Hydralazine—"L.E." syndrome —8%.[14] Hexamethonium—pulmonary fibrosis—rare
Reduction of blood pressure may lead to reduction of blood flow in vital organs	Occasional	Rare	If vascular sclerosis minimal and blood pressure reduction gradual and not too severe, local circulatory adjustments occur so that vascular perfusion is not reduced in critical areas on chronic therapy
Inconvenience and side effects of continuing therapy	Minor	Major	Aim at greatest reduction in blood pressure compatible with normal living. Sympathectomy, Rauwolfia, salt restriction —less onerous; methonium, Hydralazine, veratrum—more difficult to maintain

hypertension is necessary to make this diagnosis. Usually the hypertension is "benign" and slight azotemia, if present, is well tolerated. During acute nephritis or in terminal renal insufficiency the disease may simulate "malignant" hypertension.

Treatment is largely palliative. In acute nephritis modest elevations of blood pressure may precipitate convulsions, coma or heart failure. In these instances acute reduction of blood pressure with protoveratrine, arfonad®[6] or hexamethonium may be dramatically effective. Methonium compounds are the last choice because they may be erratic in action, precipitate collapse and are not readily excreted through the damaged kidney.

6. Hypertension Secondary to Toxemia of Pregnancy. The diagnosis here is usually based on a rising blood pressure in the last half of pregnancy accompanied by more than usual weight gain and increasing albuminuria. It is important to distinguish this from pregnancy in a patient with essential hypertension, since this latter state is far too often considered *per se* to indicate the necessity for interruption. Great psychologic harm is often done a mildly hypertensive woman by denying her a trial of pregnancy. Known prepregnant hypertension or mild hypertension discovered before the first half of pregnancy which is not progressive and not associated with albuminuria is probably benign. Steadily rising pressures, excessive edema and increasing proteinuria are signs of superimposed toxemia, which occurs with increased frequency in hypertension (50 per cent). If such a state persists for more than four to five weeks, permanent maternal hypertension or exacerbation of pre-existing hypertension is apt to occur with serious consequences.[6] Since fetal death rates are also high, the pregnancy should be terminated as soon as feasible. During this four to five week interval treatments of choice are: (1) 200 mg. sodium diet; (2) veratrum, parenterally or orally as indicated[8] and

(3) possibly hydralazine.[9] Methonium compounds may control the blood pressure but may also harm the fetus.[10]

7. Hypertension Secondary to Unilateral Renal Disease. Formerly this was usually defined as hypertension associated with a significant unilateral pyelographic abnormality although the recent report of Howard[11] indicates that more subtle unilateral defects may exist. For most practical therapeutic purposes, however, it must be established that the damaged kidney is seriously impaired in function and that its mate alone can adequately maintain excretory function. There must be no nitrogen retention. Survey for significant pyelographic abnormality is most productive in the young, and in the elderly in whom severe hypertensive disease has recently occurred.[3] If every hypertensive patient is examined, the frequency of important unilateral abnormalities is about 5 per cent and the incidence of significant improvement after nephrectomy about 50 per cent.[12]

8. Other Causes of Hypertension. More rarely, elevation in blood pressure occurs with aortic insufficiency, after acute bulbar poliomyelitis or as a result of pheochromocytoma. These and other rare forms of hypertension have been dealt with elsewhere.

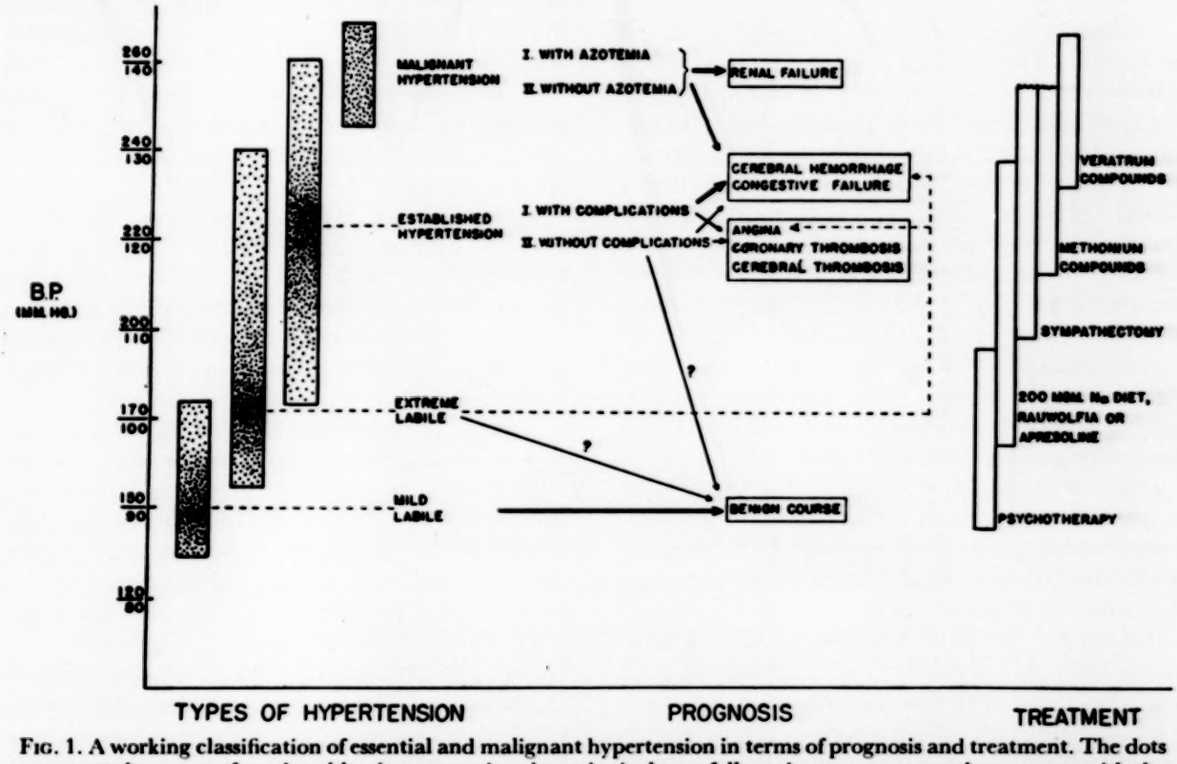

FIG. 1. A working classification of essential and malignant hypertension in terms of prognosis and treatment. The dots represent the range of random blood pressures in a hypothetical case followed over many months or years, with the usual or most frequent readings represented by the highest concentration of dots. Any type may change to a more severe stage. Transition to a more benign phase is unlikely. Established hypertension is so called because when these blood pressure levels are reached, a trend upward or downward rarely appears, unless a malignant phase is entered.[15] This category is divided into individuals with and without evidences of cerebral, renal or cardiac lesions which are the major determinants of prognosis.

THEORETIC BASIS FOR REDUCING THE BLOOD PRESSURE IN HYPERTENSION

Except as indicated in the preceding section, we have no certain knowledge of the causes of "essential" and "malignant" hypertension. Hence no rational treatment can be devised. We do recognize certain good and certain bad consequences of reducing elevated blood pressure. These are summarized in Table I.

EMPIRICAL CLASSIFICATION OF HYPERTENSION FOR PURPOSES OF TREATMENT

A working classification of hypertension in terms of prognosis and treatment is presented in Figure 1. Patients with established hypertension can be divided into those with cerebral, cardiac or renal complications (mortality 80 per cent in

ten years) and those without such complications (mortality 20 per cent in ten years).[15]

TREATMENT PROCEDURES

A. Continuously Acting Procedures

1. Surgical Sympathectomy. The *mode of action* is unknown. The prompt vasodepression which follows section of the splanchnic chain suggests that increase in vasomotor tone in a large visceral area is important (but not necessarily causative) to maintenance of the hypertensive patient's blood pressure. The gradual postoperative return to preoperative levels suggests that compensatory mechanisms are responsible for the failure of surgery to lower the blood pressure significantly.

Contraindications: These include (1) operative risks, namely, uremia, congestive heart failure, recent cerebral accident, angina pectoris; (2) generally patients over the age of fifty or with a history of thrombotic accidents; (3) technical complications such as obesity, spine deformity and chronic pulmonary disease; (4) recurrent abdominal disease, especially peptic ulcer (relative contraindication only).

Indications: Surgical sympathectomy is indicated in (1) established hypertension with vascular complications present or impending. The history of subarachnoid hemorrhage, encephalopathic episodes and early congestive failure are particular indications. (2) Another indication is established hypertension without vascular disease or progression particularly when (*a*) blood pressure is very high, (*b*) symptoms, especially headaches, are prominent, (*c*) disease originated in toxemia of pregnancy[16] or with pyelonephritis, (*d*) patient demands maximal "insurance" against complications of hypertension or toxemia of pregnancy[16] or is by temperament unsuited or unresponsive to prolonged medical management. (3) Early malignant hypertension in the preuremic stage is a third indication.

Technic: We favor the most extensive sympathectomy which can be accomplished at a one-stage operation. More extensive sympathectomies impose greater economic hardships and greater morbidity. They may, however, improve the results considerably from the 30 per cent of significant one-year reductions observed with the Peet procedure (D_8–D_{12} bilateral) to 60 per cent with total sympathectomy as performed by Grimson.[18]

Results: It should be noted that no surgical procedure often "cures" but that all lower the blood pressure somewhat and relieve cerebral symptoms in a high percentage of cases. Improvement maintained to one year usually persists. This is the only procedure which can be shown to influence mortality rates favorably and is the only treatment which does not require the patient's cooperation beyond the initial consent to surgery. It improves the efficacy of other treatments such as salt restriction and adrenalectomy.

2. Dietotherapy. The *mode of action* is unknown. It does appear, however, that body sodium stores need depletion and that renal conservation of this ion is so efficient that often such depletion cannot be achieved and the least departure from the low sodium diet serves to replete the sodium pool.[19]

Technic: Most authors believe that the rice diet of Kempner is unnecessarily restrictive since the addition and subtraction of sodium alone will raise and lower the pressure in a patient responding to the Kempner diet. The low protein content of the diet is recognized as advantageous in uremia. The low fat content lowers blood cholesterol somewhat and may in some way reduce the accelerated rate of atherogenesis in hypertension. However, as a practical matter, few persons will accept this treatment away from such centers as Durham where the group dynamic effect assists the individual in adherence to the regimen.

At the University of Michigan the 200 mg. Na diet is prescribed. Timed overnight urine samples are brought in by the patient every two weeks for six visits. The chloride content of the urine is titrated[20] and should not exceed 500 mg./24 hours. Blood pressure determinations over a three-month period serve as a check on progress.

We have not had successful results with various adjuvants to this regimen, such as resins.[21,22]

Indications: There are no contraindications except advanced renal failure. In severe cases too great a reliance should not be placed on diet alone since patients often are satisfied that "something is being done" and reject further advisable measures, especially sympathectomy.

Results: Reduction in blood pressure which can certainly be attributed to diet rather than patient-physician relationships are of uncertain frequency but probably occur in 20 to 30 per cent of cases.[23] In actual and impending con-

gestive failure the effect may be dramatic. Headache, dizziness and angina are often improved, especially in the elderly. Weight loss and weakness may develop during the initial period of salt depletion when renal conservation is insufficient.

puzzling but speaks for a specific rather than a non-specific sedative action since a tranquilizing effect regularly occurs with sufficient dosage while blood pressure reduction is seen in a lesser percentage.

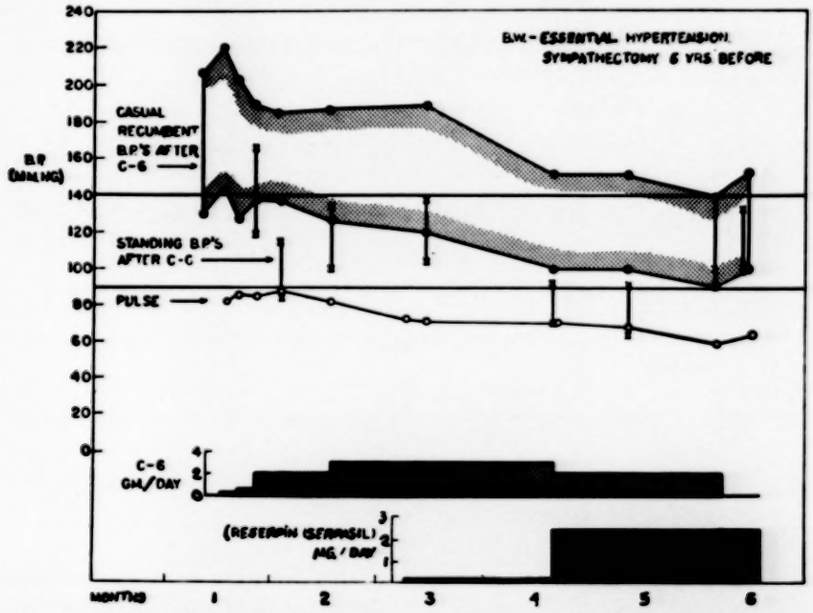

FIG. 2. Combined treatment with hypotensive drugs. Note that the depressor effect is largely attributable to the delayed action of Rauwolfia since hexamethonium could finally be reduced and discontinued without a major rise in blood pressure.

Some people do not reach a "steady state" and severe weakness, nausea and azotemia may appear. This is particularly true when the initial renal function is less than 50 per cent of normal.

3. Rauwolfia Alkaloids. The *mode of action* of these agents, whether purified (reserpin) or in cruder mixtures, have common actions which by inference suggest (1) sympathetic inhibition, such as nasal stuffiness, blood pressure decline; (2) parasympathetic stimulation, namely, bradycardia blocked by atropine, increased bowel motility; (3) non-specific, probably hypothalamic effects such as increased appetite, tendency to gain weight and languor.

Technic: Optimum dosage is unsettled but it should be sufficient to produce minor degrees of nasal stuffiness and bradycardia. This usually lies between 0.3 and 0.75 mg. daily taken in single or divided doses. Response to treatment may be delayed as long as four to six weeks. If an effect on the blood pressure is secured and the treatment is then discontinued, the side effects may stop immediately but the blood pressure rise may take several weeks. This dissociation between depressor and other side effects is

Indications: This form of treatment has no known contraindications except the relative ones of obesity and fatigue, each of which may be worsened by the side effects of the drug. It is indicated as a mild form of treatment in all types of hypertensive disease and particularly in the elderly. It is particularly useful in the "diencephalic" form of extreme labile hypertension, in which case the nervousness and blotchy eruption after histamine or exposure may be suppressed. It does not inhibit cold pressor hyperreactivity but it may moderate the excessive pressor responses to environment, except perhaps indirectly by reducing the patient's hostility to adverse situations.

Another use is in combination with methonium drugs, in which case its gastrointestinal stimulation helps or with hydralazine when it inhibits the tachycardia induced by hydralazine. The depressor effect, when apparent, is usually additive but may be of such major usefulness that the original drug may be eliminated entirely. (Fig. 2.)

Results: The drug has had adequate trial in this laboratory in fourteen cases. Table II

summarizes our specific results. It will be seen that while dramatic effects occasionally occur, the response is usually moderate. The reduction in pulse rate and gain in weight should also be noted.

oral dosage initially increased renal blood flow and lowered blood pressure but on repeated testing after two to three months of continuous treatment this effect was no longer so apparent and the casual blood pressure prior to each day's

TABLE II

EFFECT OF RESERPIN THERAPY IN ESSENTIAL HYPERTENSION*

	Time (mo.)	Final Daily Dose (mg.)	Recumbent Blood Pressure		Pulse		Weight		Remarks
			Before	After	Before	After	Before	Change	
			(mm. Hg)		(rate/min.)		(lb.)		
K. Sh.	4	0.75	172/106	−32/−24	70	−24	126	2	Less tense
D. Ba.	4	0.50	174/106	−26/−24	136	−44	132	2	Diencephalic flush relieved
S. Ci.	3½	0.2	170/108	−36/−22	60	No change	170	5	BP rise with placebo; developed angina
D. Whi.	4	1.5	197/123	17/−21	92	−16	116	1	Aortic insufficiency; tension, palpitation gone
G. Rey.	6½	0.3	188/120	−28/−20	80	−20	168	−3	.....
C. Pe.	3	0.5	176/104	−12/−14	90	−26	123	12	.....
G. Kr.	4	0.4	198/132	−22/−14	116	−32	87	5	Little tension relief
G. Fa.	4	0.3	192/126	10/−10	84	−20	155	3	C-6 therapy also given
D. Wa.	5	0.3	238/126	8/−2	76	−12	162	18	.....
J. Ai.	5	0.75	185/100	5/0	64	− 8	169	5	.....
G. Red.	5	0.75	180/128	46/4	88	−20	136	15	Combined with C-6
L. We.	7	1.0	254/109	−24/5	76	−16	126	7	Tension relieved
R. Abr.	4	0.3	208/110	12/6	78	− 2	176	15	.....
G. At.	3	0.75	183/96	9/8	68	− 4	161	6	.....

* All patients followed more than three months are included. Observations before and after treatment represent the single casual recumbent readings on admission to the clinic. Final daily doses are those now being used, but not necessarily starting or minimum sustaining dose. Cases are arranged in order of blood pressure response. It will be seen that other indices of Rauwolfia effect do not run parallel to depressor effects.

Toxic effects have been infrequent. Occasionally patients complain of excessive fatigue and dyspnea but reduction of dosage gives relief.

B. Intermittently Acting Procedures

1. Hydralazine. The *mode of action:* Although introduced as a centrally acting vasodilator,[24] the bulk of physiologic evidence favors a direct vascular action producing widespread vasodilatation and increased blood flow in kidney, extremity and splanchnic areas with a compensatory rise in cardiac output. The flush, excitation and widened pulse pressure resemble the effects of hyperthyroidism or fever superimposed on the hypertensive state. The unusual renal vasodilator action was recently investigated in our laboratory. The drug given in tolerable administration of the drug was not reduced. Hence the induction of renal hyperemia had not altered the hypertensive state except transiently and the drug is to be considered only an unusually efficient vasodilator.[25]

Technic of treatment: Side effects being prominent, we prefer very gradual increase in dosage from 10 mg. four times daily toward upper limits of 75 to 100 mg. doses. Higher levels are rarely well tolerated and may be more likely to lead to the lupus erythematosus syndrome.

Indications: The hydralazines appear to be indicated in established hypertension with or without complications except angina and heart failure in which cardiac stimulation may be undesirable.

The drug has been suggested for cerebral complications.[26] Unfortunately it does not in-

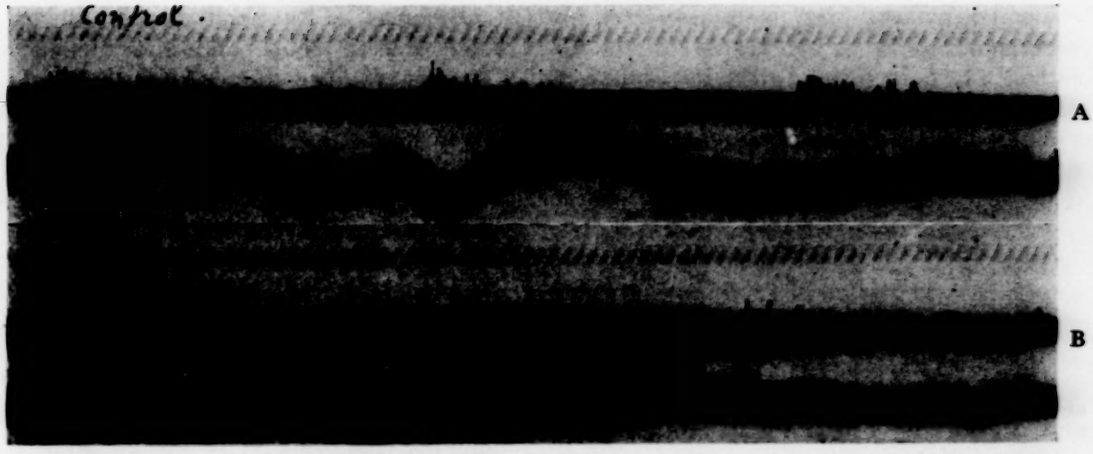

FIG. 3. Effect of protoveratrine in increasing afferent discharges and decreasing efferent outflow through the splanchnic nerve. The upper half of each tracing is taken from the carotid sinus nerve of a cat; the lower half from the right major splanchnic nerve. A, note the burst of pressoreceptor activity of the carotid sinus nerve, synchronous with systole, and the irregular activity of the splanchnic. B, after 3 μg./kg. protoveratrine, note the intensified and more or less continuous discharge of the carotid sinus afferent fibers resulting in inhibition of splanchnic efferent impulses. (Recording furnished through the courtesy of A. S. Dontas, M.D., Department of Pharmacology, University of Michigan Medical School.)

crease cerebral blood flow as determined by the nitrous oxide method.[27] Furthermore, I have seen four cases of thrombosis occur with treatment. Although the drug did not appear to cause these accidents, we are not impressed with its protective value under conditions of impending thrombosis.

Theoretically, hydralazine may be of unique benefit to patients with marked renal impairment because it produces an increase in renal blood flow. However, the rate of glomerular filtration is not increased, so the removal of excretory products is not hastened in these individuals. Any benefit derived from renal vasodilation must be due to the improvement of blood supply to the renal tubular cells. This is largely theoretic and in our experience improvement in excretory function has never been clearly attributable to hydralazine alone.

Results: We have not had a wide experience with this agent but in the cases we studied carefully, significant reductions in blood pressure could be achieved in only a few patients when the maximum tolerated dose was given. On the other hand, certain patients have shown remarkable and sustained hypotensive responses. We have seen the arthritic complication described by others[14] in one patient. This serious side effect certainly deserves consideration but it is hoped that by restricting the total daily dosage it will not be seen frequently.

2. Veratrum Compounds. The *mode of action:* Veratrum derivatives possess the ability to produce an after-discharge in the nerve after each normal discharge. Thus at a critical threshold the number of normal discharges may be multiplied. Afferent stimuli from the carotid sinus and coronary artery receptors which maintain control of blood pressure and pulse rate through central connections are thus increased when veratrum concentrations about the nerve fibers reach a critical level. Figure 3 illustrates this mechanism of action.

The following clinical observations are thus explained: (1) A threshold effect in that insufficient doses produce no detectable effects until repetitive discharges are created in the centripetal innervation; (2) receptor adjustments to intrasinus pressure and other stimuli remain intact so that orthostatic hypotension does not occur. Respiratory arrhythmias may persist or even become intensified. (3) Peripheral adjustments are made by the activation or inhibition of normal efferent pathways which have not been certainly identified. These pathways are universally present and when sufficient veratrum is given the blood pressure and pulse rate of every patient can be reduced. (Fig. 4.) Blood pressure reduction comes about apparently as a result of a modest decline in cardiac output and an evenly distributed reduction in peripheral resistance.[28] Intimately associated with the central action of the drug is an emetic effect apparently initiated by a direct action on the cells of the nodose ganglion. This unfortunate action limits the effectiveness of what would

otherwise be the ideal drug for the treatment of hypertension.

Technic: The drug may be given intravenously in acute emergencies and if too great a reduction in blood pressure is not sought freedom from emesis can be achieved. Meilman recommends

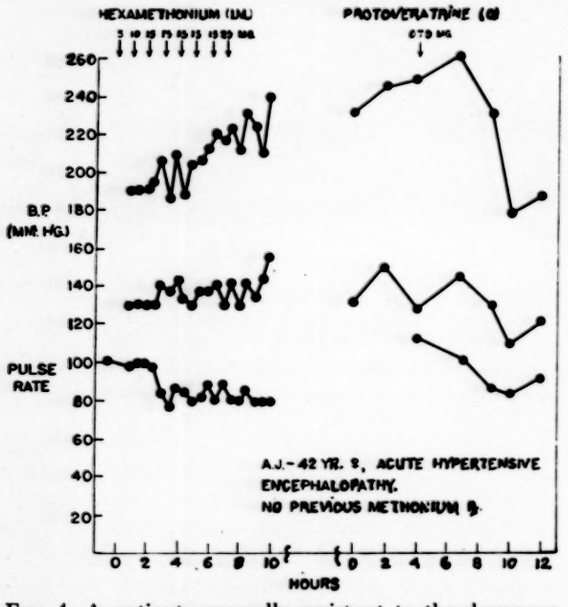

FIG. 4. A patient unusually resistant to the depressor effects of parenteral hexamethonium showed, on the following day, an excellent hypotensive response to veratrum with decided clinical improvements.

administration of protoveratrine at the initial rate of 1 μg./kg./min., adjusting to tolerance as the desired effect on blood pressure is secured.[29] If given orally the critical level for emesis may easily be surpassed. For this reason we have recommended a large loading dose taken after breakfast and supper and a second "booster" dose of 0.25 mg. two hours later if nausea or substernal distress has not been so prominent from the initial dose as to suggest too great absorption into the emetic range. In this way the patient may control emesis by omitting the "booster" doses according to subjective effects. The morning and evening initial doses must be determined by trial and error but usually range between 0.75 and 1.5 mg.[30] It is possible that certain veratrum alkaloids will have a superior emetic/therapeutic ratio. Cryptenamine has recently been reported to be superior to protoveratrine in animal assay but the clinical differences appear slight.[31]

Indications: Because of the bradycardia and possible positive inotropic action the drug is especially useful in cardiac hypertensives with tachycardia. Treatment should not be instituted during acute digitalization since both drugs have vagomimetic effects and heart block may ensue. Veratrum block can be relieved instantly by 1 mg. atropin sulfate given intravenously.

The drug is very effective in lowering the blood pressure in renal failure and the effects are more predictable than with methonium which may be poorly excreted. It is therefore preferred in the palliative treatment of chronic hypertension with azotemia, and in acute convulsive episodes seen in acute or chronic nephritis. It likewise has value in the treatment of eclampsia and pre-eclampsia in which methonium compounds may be toxic to the fetus.[9]

Because blood pressure reduction with a tolerable regimen is intermittent and invites nausea, we now believe that oral methonium compounds are more likely to reduce blood pressure and to be acceptable to the average patient with established or malignant hypertension and adequate renal function.

No special contraindications exist except those which might apply to any hypertensive agent, namely, avoiding its use in atherosclerotic patients in whom thrombotic complications are a definite risk.

Results: These have been detailed elsewhere.[30] From 40 to 60 per cent of patients on a meticulously regulated regimen will have four to eight hours of significant blood pressure reduction daily with infrequent nausea or vomiting. Although this is not an impressive quantitative effect, the clinical responses seem to be favorable in many instances.

3. Methonium Compounds. The *mode of action* in blood pressure reduction in the recumbent position is a result of inhibition of sympathetic vasomotor tone (autonomic ganglia). Orthostatic reduction, which is always greater, is probably the result of added venous pooling from loss of venomotor tone, reduced venous inflow and decreased cardiac output.[32] This reduced output is apparently distributed judiciously through local vascular homeostasis, so that cerebral, renal and splanchnic flow are not greatly reduced. In impending cerebral ischemia or azotemic states these adjustments may be faulty. "Tolerance" occurs rapidly so that, in our experience, only excessive doses will lower recumbent blood pressure after several months of therapy although orthostatic effects usually persist when the dose is sufficiently increased.

The mechanism of "tolerance" unfortunately does not extend to the parasympathetic innervation, so that a dose large enough to affect the blood pressure satisfactorily may be too great to allow normal peristalsis, even with laxatives, and treatment may have to be abandoned on these grounds. "Tolerance" is a very interesting phenomenon and appears to represent a compensatory process since sympathetic vasomotor tone remains inhibited at the time tolerance appears.[33]

Technic: In acute emergencies hexamethonium may be given intravenously at a rate of 1 mg. per minute with constant blood pressure control by the technic recommended by Freis.[34] Patients with increased cerebrospinal fluid pressure or uremia may be very sensitive and overshooting may easily result.

Early in the control of severe hypertension, especially when slight uremia is present, the drug must be given precisely and only by the parenteral route so as not to secure excessive blood pressure reduction, thus further impairing glomerular filtration and excretion of the injected drug. At this stage blood pressure must be constantly monitored and doses selected to avoid too great depression and yet keep up with increasing "tolerance." A four-hour schedule is advised beginning at 5 mg. and altering each subsequent dose up or downward by 5 mg. until the desired control is achieved. In our hands this program is rarely successful in chronic outpatient management of all but the most advanced cases because it involves too much inconvenience to the patient and after each injection a period of orthostatic disability is imposed. In this connection the longer-acting "Ansolysen" is of great value.[35] Two injections a day will usually produce reasonably satisfactory orthostasis although a longer period of blurred vision may occur and more rest after each injection may be required. The drug is five times as potent as hexamethonium and, in changing over, this factor must be considered. At present we prefer this agent in parenteral therapy, which we use in the management of hypertensive crises and in patients refractory to various oral combinations.

Oral administration of hexamethonium is recommended when possible. Dosages increasing from 125 mg. three times daily after meals and at bedtime to 750 mg. are given as necessary to reduce standing systolic blood pressure to 110–120, if well tolerated, and at least to 160–180. A daily saline or irritative laxative is given. The patient is instructed, as advised by Smirk,[35] to stand motionless for one minute before taking each dose. If the previous dose of the drug has been so effective that dizziness occurs, the intended dose is halved. If constipation persists more than twenty-four hours, treatment is stopped until a bowel movement occurs. Single oral doses of more than 750 mg. are never exceeded. On this regimen we have had no serious intestinal complications and have achieved a reasonably reproducible blood pressure decline. Rauwolfia is prescribed concomitantly, and occasionally hydralazine is also added.

The longer-acting less vagolytic compound known as M & B 2050A has recently become available in this country as "Ansolysen." It appears slightly superior in smoothness of action and in producing less constipation (Table III.)

Indications: Extreme labile hypertension has not been satisfactorily affected. The doses necessary to inhibit vasopressor rises are unfortunately too high to be readily tolerable in prolonged therapy. We hesitate to initiate this treatment in established uncomplicated hypertensive disease in view of the difficulties inherent in chronic management. The continuously acting depressor procedures are preferred; but if they are ineffective, the patient's pressure is very high and he desires a therapeutic trial, we are willing to proceed.

Established hypertension with cerebral or cardiac complications or malignant hypertension without uremia are indications for vigorous methonium-Rauwolfia therapy since the prognosis in these cases is guarded. Even here we prefer a trial of sympathectomy first when possible.

Contraindications: These include uremia (NPN over 60 mg. per cent), pulmonary disease (when drying of bronchial secretions may be harmful), prostatic hypertrophy and arteriosclerosis generally, in which induced hypotension may induce thrombotic accidents. Older patients are markedly sensitive to therapy; but if they tolerate hypotension well, they should not be excluded particularly if they represent cases of essential hypertension extending into later years rather than simply arteriosclerotic (systolic) hypertension.

Results: It is extremely difficult to present an objective evaluation of the long-term effects on the blood pressure. The experience in our clinic is presented in Table III. Recumbent blood pressures have been little affected. Day-

TABLE III

TREATMENT OF CHRONIC HYPERTENSION WITH ORAL GANGLIONIC BLOCKING AGENTS

Patient	Age	Final Daily Dose (gm.)	Time (mo.)	Blood Pressure				Remarks
				Recumbent		Standing		
				Before	After	Before	After	
				(mm. Hg)	(Δ mm. Hg)	(mm. Hg)	(Δ mm. Hg)	
Oral Hexamethonium								
F. Sh.	61	1.75	4	220/129	−29/−41	220/140	− 61/−49	Retinopathy and decreased vision; improved on therapy
F. Ha.	38	3.0	3	179/125	−19/−20	173/127	− 43/−29	.....
L. Di.	58	2.5	3	220/138	−35/−24	202/133	− 36/−18	Prior CVA with recovery; asymptomatic on therapy
V. Je.	45	2.5	3	197/122	−13/−12	185/121	− 23/−16	.....
H. Le.	32	1.0	8	199/126	−36/−16	186/125	− 30/−15	.....
A. Le.	47	1.0	6	164/112	− 3/−9	155/110	− 26/−15	Ligated intracranial; AV fistula
M. Ma.*	43	1.25	8	240/134	−70/−33	190/129	− 87/−54	2 encephalopathy attacks before therapy
M. Po.*	49	2.5	6	193/138	− 6/−14	182/133	− 72/−44	Encephalopathy and heart failure prior to therapy
S. Ch.*	33	2.0	6	276/151	−36/−9	219/146	− 44/−34	Malignant; died in uremia
M. T.*	44	2.5	3	195/131	−33/−25	164/125	− 38/−30	.....
D. Or.*	44	1.5	7	211/129	−25/−11	188/129	− 46/−24	.....
J. Be.*	51	2.5	6	250/134	−52/−11	201/128	− 43/−22	Angina improved slightly
B. Ko.*	44	1.4	2	229/122	−40/−14	193/119	− 63/−20	.....
A. Ch.*	48	1.75	6	151/106	25/−2	138/97	− 8/−18	Early malignant retinal changes improved
J. Ph.*	46	1.0	10	219/137	−35/−7	181/126	− 39/−17	Died sudden death −?; cardiac standstill
R. Fo.*	33	3.0	7	218/136	14/−5	191/135	− 28/−15	See also below
N. Tr.*	39	3.0	10	190/106	14/5	168/99	24/10	.....
G. Re.	36	1.25	7	199/134	−29/−27	206/151	−110/−85	Reserpin produced additive effect: hence C-6 dose reduced
B. Wi.	37	3.0	3	209/137	−82/−51	196/142	− 97/−68	Same as Patient G. Re.
G. Fa.	44	2.5	10	191/119	0/−6	154/110	− 11/−17	.....
Oral Pentamethylene Pyrrolidinium Bitartrate, "Ansolysen"								
A. He.	41	.025 subc.	3	247/130	−78/−35	207/133	− 81/−49	600 mg. ineffective; injects self twice daily
C. Pe.	42	0.54	2	192/121	−44/−23	180/120	− 71/−37	.....
C. Be.	43	0.6	3	206/148	−18/−32	.....	− 24/−31†	.....
A. Av.	45	0.6	3	189/115	−20/−15	.....	− 62/−30†	.....
B. Ko.*	44	0.24	1	224/122	−14/−3	193/119	− 17/−8	.....
F. Fa.	37	0.42	2	204/121	−11/0	200/126	− 5/2	.....
R. Fo.	33	0.45	1	223/122	6/3	157/113	21/12	Converted to C-6

* Splanchnicectomy (D_5-D_{12}) done usually three to twelve months before observations started.

† Referred to pretreatment recumbent blood pressure.

Readings recorded represent average of half-hourly readings throughout clinic day (9 A.M. to 4 P.M.) before or at time of last visit. Drugs taken in divided doses after meals and at bedtime (C-6) or at 7-3-10 daily (ansolysen). All cases followed more than three months are listed except with ansolysen in which all patients followed more than one month are recorded.

It will be seen that in general, significant reductions are largely in the orthostatic blood pressure, and that sympathectomy has not rendered the patients more sensitive. When reserpin has been effective (G. Re., B. Wi., G. Fa.), C-6 doses have been lowered because of decline in the day's starting blood pressures rather than in any particular synergism. In one instance, (B. W.), it has since been possible to omit the C-6 entirely without a resurgence of the blood pressure.

Ansolysen was superior in that fewer parasympathetic blocking and gastrointestinal side effects occurred and the responses were more lasting. On the other hand, patients were more refractory to oral therapy with ansolysen (on an assumed effective oral ratio of 1 : 5) as shown in the case of R. Fo., B. Ko., who were converted to C-6 with better results and A. He., who was sensitive to parenteral management only.

The spontaneous changes in blood pressure that might have occurred over the time indicated are unknown. The orthostatic effects plus occasional observations when drug was stopped suggest, however, that the reductions are due to drug therapy. Dosage arrived at was amount tolerated without severe gastrointestinal or syncopal effects, and after three months rarely required further increases.

time ambulatory blood pressures in the clinic are probably reasonably representative of day-to-day effects as judged by the occasional patients who bring in blood pressure reports taken by relatives or physicians. It is probable that daytime blood pressure levels are usually kept under good control. Mortality has so far been low in the nonmalignant group but two patients under good control have died of unknown cause, not the direct result of therapy. It has been an important part of our program to keep the treatment acceptable. As a result we rarely succeed in inducing strict normotension but our patients' life and work are rarely adversely affected beyond impotence and a certain degree of easy fatiguability.

Despite these modest objectives the individual results, particularly in cases with cardiac and encephalopathic histories, have been so impressive in both acute and chronic terms as to encourage us to push treatment into the field of prophylaxis against these accidents in established hypertensive patients with maintained blood pressure levels in the range of 220/120 or above. Future mortality statistics alone will confirm whether this course of action is justified.

SUMMARY

1. The commoner causes of hypertension are defined and the treatment of each is indicated.

2. The clinical types and prognosis of essential and malignant hypertension are presented.

3. The indications for and contraindications to depressor treatment are summarized.

4. Treatment of severe established hypertension without complications and extreme labile hypertension is elective and probably should include those procedures likely to have a long-sustained effect with a minimum requirement for day-to-day management. These include sodium restriction, sympathectomy and reserpin.

5. It is concluded that more vigorous therapy for established hypertension associated with certain vascular complications and in the malignant stage is justified and should include, in addition to the foregoing, the selective use of hydralazine, methonium and veratrum.

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Conference on Therapy

Selection of Digitalis Preparations and Their Proper Administration

THESE are stenographic reports, which have been edited, of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: Several years have elapsed since the last time we considered in these conferences the topic which has been planned for today, namely, the choice of a digitalis preparation. This is a kind of problem which keeps recurring without end. That it should be so is quite natural, for many old issues remain unresolved and new issues arise with the introduction of new preparations. What may once have been the preparation of choice may now be superseded by others. Dr. Luckey will lead off the discussion.

DR. HUGH LUCKEY: I am not quite sure why I am the one who was asked to open this discussion since basic work in the pharmacology of digitalis has been done by others in this institution and there are others here who can probably speak of it with considerably greater authority. I suppose what I am expected to do is to give an account of our clinical experience in the expectation that it will raise enough questions to get the conference under way.

The place of digitalis in cardiac therapy has not changed materially over the years. With the exception of sedatives, it is still the medication most frequently used in the treatment of patients with congestive failure. Although some doubt has been raised about this point with the more intensive use of diuretic therapy, I still believe that digitalis medication is the most important measure in the management of congestive failure. It is employed for the purpose of correcting the abnormal blood flow and pressure relationships which develop in congestive failure. The bulk of the evidence points to a direct action on the heart muscle which increases the contractile force of the heart and enhances the cardiac output. It is used in heart failure irrespective of the underlying cause. There are very few contraindications to its use. It is of course self-evident that one should not add more of a digitalis preparation when the patient is already overdigitalized with another. A patient with ventricular tachycardia in failure also presents a relative contraindication. Digitalis may be injurious in the presence of this abnormal rhythm.

Aside from the case of congestive failure, we use digitalis preparations to control certain abnormal rhythms, especially auricular fibrillation, in which the drug is used to slow down the ventricular rate. Then there are such abnormal rhythms as paroxysmal auricular tachycardia, A-V nodal rhythm, and auricular flutter. I may mention the fact that in the last hundred patients with auricular flutter whom we have treated with a digitalis preparation a normal sinus rhythm was established in forty-six without the use of any other drugs and with continuation of digitalis. In thirty-two of the one hundred patients the flutter was converted into auricular fibrillation which presented as the basic rhythm with good control of the ventricular rate. In the remaining patients of this group the auricular flutter persisted although the ventricles were controlled at a lower rate as the result of a higher degree of A-V block.

Our interest in the selection of a drug of the digitalis series arises from two possibilities, qualitative differences and quantitative differences. The question of qualitative difference between preparations of digitalis has been the subject of much discussion and debate. From our

own clinical experience, and this seems to be the experience of most others, as well as the conclusions to be drawn from experimental work, there seems to be no satisfactory proof in favor of a qualitative difference between digitalis materials. They all seem to act through a similar mechanism. The differences that are observed between one preparation and another relate to dosage, the speed of onset of effects, and the duration of action. There is still much confusion regarding dosage and it is in a large measure due to the fact that there are so many preparations and mixtures of digitalis substances. I was interested in noting a statement of William Withering in his discussion of foxglove in 1785 that "the more we multiply the forms of any medicine the longer we shall be in ascertaining its real dose." The basic dictum in regard to dosage has been stated many times before but it can bear repetition. One should give that amount of the preparation which produces the optimum benefit one is seeking without producing toxic effects. There is need for two types of digitalis preparations, one to meet the needs of the majority of patients in the treatment of congestive failure and the other for the relatively small percentage of patients who require emergency care.

We have been using digitoxin as the drug of choice in the treatment of non-emergent congestive failure. It is a fairly constant preparation and not subject to the objections inherent in the bioassay of the crude preparations and mixtures. Its actions are practically identical with those of digitalis leaf preparations both in speed of onset and duration of action. We prefer this preparation also because of the fact that in situations which require rapid treatment, although not so urgent as to need extremely rapid onset of action, one can give a large dose of digitoxin at the beginning without causing nausea and vomiting. We are guided in our observations in any particular patient by the fact that an oral dose of digitoxin produces considerable effect in about an hour, more quickly—within ten to twenty minutes—with an intravenous dose; that the peak action is reached in from six to eight hours; and that during the next two or three weeks the effect gradually wears off. It is best given by mouth. There are occasional instances in which the intravenous route is necessary. There is a preparation of digitoxin in 40 per cent alcohol which may be given by intravenous injection but should be diluted four times before injection to reduce the alcoholic content to 10 per cent. Nearly all the patients that we see can be managed satisfactorily with digitoxin. The range of doses required for adequate initial digitalization is between 1 and 1.8 mg. Very few patients require doses outside of this range and many patients, as has been well shown by Dr. Gold, can be digitalized adequately with 1.2 mg. of digitoxin. Many patients, however, especially the advanced hospital cases, require as much as 1.4 to 1.6 mg. We usually start with 0.8 mg. I have never seen toxicity from this dose. It is followed by 0.4 mg. in six hours. The interval of six hours is used because it takes as long as that to produce the full effect of the previous dose, and the result is used as a guide for adjusting the next dose. The ventricular rate in the patient with auricular fibrillation serves as a good guide to adjustments in the dose. The problem is more difficult when there is normal sinus rhythm. In these cases we also usually give a total of 1.4, occasionally 1.6 mg., at most 1.8 mg. This takes about eighteen hours. The maintenance requirement of digitoxin has been fairly well established. It lies somewhere between 0.1 and 0.2 mg. a day. Very few patients require less than 0.1 and very few more than 0.2 mg. A daily maintenance dose of 0.15 mg. has become fairly popular and one of the firms has now prepared a tablet of this size.

As far as we can observe, the toxic manifestations of overdosage of digitoxin are identical with those of digitalis. Loss of appetite is the first effect. It is soon followed by nausea and then by vomiting. Ventricular premature contractions and prolongation of the P-R interval in the electrocardiogram also occur. It has been said that digitoxin is particularly prone to produce toxic rhythms but this has not appeared in our experience.

The kind of patients whom we encounter at Bellevue Hospital make it necessary for us to have on hand a preparation of the digitalis group more suitable for the acute emergency. I refer particularly to the case of acute pulmonary edema, often with very rapid auricular fibrillation. Ouabain has here been the drug of choice for this purpose during the past thirty years, perhaps longer. Most people seem to think of this as a very toxic drug. I believe this reaction is the result of some traditional misconception. We find it perfectly safe. The intravenous injection produces effects within a few minutes and the maximum action of a dose develops in about an hour. In the patient who has not had a digitalis

preparation recently, we start with 0.5 mg. which is equivalent to 5 cat units. This is followed within an hour, if toxic effects have not been observed, by 0.25 mg. An hour later a dose of 0.1 mg. may be given. The administration of these additional doses depends, of course, on the evidence of therapeutic effect and toxic signs. There then comes the problem of shifting over to a more persistent preparation. There are many ways of doing this. One which we have found satisfactory is to give, at the time of the last intravenous dose of ouabain, 0.4 mg. digitoxin by mouth, and follow this by two more doses of 0.4 mg. at intervals of eight hours. As in the case of all digitalis medication, adjustment in this routine is made in accordance with the signs of therapeutic or toxic effects. After the patient is digitalized in the manner I have just described we carry the treatment along with a daily dose of 0.15 mg. of digitoxin.

We have had no need for using any other members of the digitalis series. I think it is a mistake to shift from one to another among the wide variety of digitalis preparations that are available.

DR. GOLD: Dr. Luckey has made several statements concerning the choice of a digitalis preparation. He leaves no doubt about his position in the matter. We know, of course, that there are many who would take issue with Dr. Luckey on some of his points. We are now ready for comments and questions.

DR. JEROME SILVERMAN: I would like to ask what Dr. Luckey would do in the case of a patient who has received digitoxin within the past few days and who then goes into acute pulmonary edema. How would you manage the matter of ouabain dosage in such a case?

DR. GOLD: Before you answer that question, Dr. Luckey, you should ask Dr. Silverman another question.

DR. LUCKEY: I suggest that you ask the other question.

DR. GOLD: Very well. How well digitalized is the patient with digitoxin to whom he referred at the time pulmonary edema develops? Whether you judge the patient to have been fully digitalized with digitoxin and to have gone into pulmonary edema in spite of it, or whether you judge the patient to be under the influence of very little digitoxin at the time that the pulmonary edema occurs, would have something to do with the way Dr. Luckey answers the question.

DR. LUCKEY: I think I know why Dr. Silverman asked that question. It is commonly stated that ouabain should not be used after digitoxin unless the digitoxin was discontinued two weeks previously. If we do not know the status of the patient in acute pulmonary edema with respect to previous digitalis medication, we proceed more cautiously in the use of ouabain. Where there is a rapid ventricular rate in auricular fibrillation in the absence of thyrotoxicosis or fever, we have no hesitation in giving 0.25 mg. ouabain intravenously even if the patient is under the influence of one or another preparation of digitalis. In a patient who has had digitalis recently, the more usual practice is to give digitoxin 0.4 mg. every six hours, being guided again by the appearance of therapeutic or toxic effects.

DR. SILVERMAN: Would you give the digitoxin intravenously?

DR. LUCKEY: Not if the patient can take it orally.

DR. SILVERMAN: Would you give it orally if the patient were in pulmonary edema?

DR. LUCKEY: If the onset of the effect is just as rapid by mouth, there is no advantage in giving it by vein.

DR. GOLD: There is some advantage in giving digitoxin by vein in an acute emergency, if one decides to use this drug in such a case. The initial effects come on much more quickly by the intravenous route. I should like to comment on Dr. Silverman's question. If pulmonary edema develops while a patient is under the influence of a digitalis preparation, the prevailing situation may be one in which the patient has been adequately digitalized, but in spite of it pulmonary edema develops, or the patient has gone into pulmonary edema because he has not had enough. If there is evidence of a high degree of digitalis action, as, for example, heart block or very slow ventricular rate in auricular fibrillation, or premature contractions, or nausea and vomiting, it is well to assume that the patient has had as much digitalis as is advisable, or has even had an overdose, and that even full digitalization was not sufficient to prevent the attack of pulmonary edema. Nothing is to be gained by giving more of a digitalis material, not to speak of the danger of doing so. On the other hand, if there are no toxic effects, if there is a rapid heart rate with auricular fibrillation, or a rapid sinus rhythm, it would be wise to assume that the patient has not had enough of the previous digitalis material and to proceed to use

ouabain intravenously in the endeavor to clear the pulmonary edema. In such a case, the dose which Dr. Luckey mentioned, 0.25 mg., may be safely given at one time. Such a dose will not produce serious toxic effects in a patient who shows no toxic effects, irrespective of the amount of a digitalis material he has had before. This dose may then be repeated at intervals of an hour in the manner in which Dr. Luckey mentioned, being guided by the evidence of action. I think it is a safe assumption to make that if the patient shows no toxic effects an hour after an intravenous dose of 0.25 mg. ouabain, the repetition of this dose would at most cause only very minor toxic effects. Such increments of dosage given in this way are perfectly safe.

Dr. John S. LaDue: I might supplement these remarks by an observation we made some time ago in a group of 104 patients with congestive failure. They were all receiving full maintenance doses of digitalis. We then gave them lanatoside C intravenously in amounts up to full digitalizing doses, 1.6 mg. In this group, toxic reactions developed in 6.7 per cent, an incidence of toxicity for this dosage of lanatoside C previously found for patients who were not under the effects of digitalis. I would not recommend this as a practice but it serves to emphasize the safety of this intensive form of digitalization.

One more point: it has been our impression that patients in frank congestive failure require two to three times as much digitalis as those in whom compensation has been established, to keep the condition in order. This may be easily observed in terms of the amount of digitalis necessary, for example, to keep the ventricular rate in a patient with auricular fibrillation at a level below 90 a minute in the two different stages of failure.

Dr. Luckey: We have had a few patients to whom we have given a dose of 0.8 mg. of lanatoside C intravenously, who had already been fairly well digitalized. There were no ill effects, but we do not have enough of these to learn how frequently ill effects would follow such a procedure. I would like to suggest that in the study to which Dr. LaDue referred the patients were only partially digitalized and it is for that reason that a full dose of lanatoside C failed to increase the incidence of toxicity.

As to your second point, I know that there are a number of factors which modify the tolerance to digitalis. One which has received special attention recently is the low plasma potassium concentration. In this state the heart seems to become more susceptible to the effect of digitalis in producing ventricular premature contractions.

Dr. Gold: I am not sure of the meaning of Dr. LaDue's observation that patients on full maintenance of digitalis were able to tolerate a full digitalizing dose of lanatoside C as if they had not had digitalis. This would be contrary to the most firmly established fact concerning the digitalis materials, namely, that their effects are additive. They did not seem to be so in the observations which Dr. LaDue mentioned. It may indeed be an illusion, due to the possibility which Dr. Luckey suggested, that the maintenance dosage in these patients which was believed to be "full" may actually have been quite light. There is the fact that there is a fairly wide margin between the minimal dose which produces the desired therapeutic effect and the dose which causes toxicity. This is an insensitive area in the dosage-response curve of digitalis action, for here the dose may be increased by 50 per cent or more without any appreciable change in the therapeutic action or any evidence of toxic action. We published several papers some years ago in which we investigated the nature of this phenomenon of the resistant portion of the dosage range.

As to Dr. LaDue's other point, that patients in congestive failure require more digitalis to get them out of it than they do to keep them out of it, it seems to me that that is a fairly well known fact. It is the basis of virtually all practice in regard to digitalization, large doses to induce the effects and small doses to maintain them. In this connection, there is the observation on which we published several years ago to the effect that patients in far advanced congestive failure often require higher degrees of digitalization to control them than the same persons need when the failure is less advanced.

Dr. LaDue: We arrived at this conclusion in a somewhat different way. We found that patients in advanced congestive failure, when fully digitalized, developed toxic effects after active diuresis was produced and the venous pressure fell. We interpreted this to mean that the intensity of digitalization required when the failure was advanced became a toxic concentration after the failure cleared.

Dr. Gold: I do not believe that I have ever seen that happen. Such a reaction has been

described as the result of the diuresis caused by the mercurial diuretics in digitalized patients. I have never seen that either.

DR. GEORGE READER: In regard to the amount of digitalis necessary under different conditions, we might point out the common experience that a patient who seems to be well digitalized when at rest will show that the degree of action is inadequate when mobilized. Clearly, under conditions of stress, more digitalis is necessary to maintain compensation.

DR. GOLD: That is familiar. Infection is another factor which places the heart under stress and often calls for intensification of digitalis therapy to maintain the patient free of failure.

DR. WALTER MODELL: I wonder if Dr. Luckey would help us to reconcile what seems like a difference in his plan of dosage for digitoxin and ouabain. In the case of ouabain he advocates an intravenous dose of 0.5 mg. at one time, which represents 5 cat units, while in the case of digitoxin he hesitates to give 1.2 mg. at one time by the oral route, although it is only about 3 cat units, and advises, I presume in the interest of safety, the use of only 0.8 mg. or 2 cat units at first, followed by 0.4 mg., the third cat unit, six hours later.

DR. LUCKEY: I suggest that this is due to the difference between cats and humans.

DR. GOLD: One would have a hard time defending that position. It is a fact that people have usually found about 1 mg. or 10 cat units of ouabain intravenously necessary to induce full effects with this glycoside and in the case of digitoxin by mouth the usual dose is only 3 or 4 cat units. These differences in experience relate to observations made under conditions that are not strictly comparable. There is little doubt in my mind that in experiments made under strictly comparable conditions the effect of a cat unit of any two glycosides given by the intravenous route would not differ much. The experience with ouabain on which these figures are based is on a series of doses and given for the most part to patients in advanced congestive failure. The experience with digitoxin is based on the single dose, for the most part used in cases of failure many of which are only mild. The series of doses of a rapidly excreted drug leads to a fairly large total dose. The far advanced congestive failure, as has already been mentioned in this conference, also requires the larger doses. These two factors, and there may be others, show the digitalizing dose of ouabain by the intravenous method to be fairly large, in terms of cat units. If only far advanced cases were treated with digitoxin, the dose would also be considerably larger than the 1.2 mg. or 3 cat units. There is also the fact that by comparison with ouabain, digitoxin is slowly excreted. This is then a second factor which tends to reduce the required dose and helps to bring out the difference in the cat unit dosage of intravenous ouabain and oral digitoxin. Some time ago we published the results in a group of patients with auricular fibrillation and failure of moderate severity in connection with a comparison of ouabain with acetyl-strophanthidin. There we found that the single dose of 0.5 mg. ouabain or 5 cat units intravenously produced the same kind of effects we had previously observed in connection with single doses of 3 or 4 cat units of digitoxin. These are more nearly comparable kinds of experiments and in these the doses of the two compounds in terms of cat units come more closely together.

DR. LUCKEY: In our observations at Bellevue we found that 0.5 mg. of ouabain was inadequate in patients with auricular fibrillation. At the end of an hour the heart rate in these cases was still well above 100 a minute.

DR. GOLD: An hour is not always long enough for the full effect. But as I have already indicated, I agree that 0.5 mg. or 5 cat units is not sufficient in the advanced cases of failure. They require more of ouabain as they require more of any other digitalis material.

DR. MODELL: I am inclined to agree with Dr. Gold that an assumed difference between the cat and man does not explain the difference in ouabain and digitoxin dosage.

DR. GOLD: In order to complete the story, it would be well to mention that there are very great differences between different digitalis materials in the dosage required in terms of cat units, but only when these materials are given by the oral route. It is to be remembered that the bioassay method calls for a comparison of two materials by the intravenous route in animals. This comparison tells nothing about one of the most important properties of digitalis materials, differences in their absorption. And so it is that two materials may have the same potency by the intravenous route, the same potency in terms of cat units or U.S.P. units, but it may take many times as much of one as of the other to produce therapeutic effects when the two are compared by the oral route. This is one of the weak spots in the intravenous method of bioassay, its failure

to reveal differences in absorption which are so important when the drugs are used by mouth.

DR. LUCKEY: The point which you made regarding the differences between the single dose and the series of divided doses is in line with the observation by Cohen and Levy some years ago. They did not happen to give 1 mg. of ouabain intravenously at one time, but 0.5 mg., repeated in an hour, and in this form of dosage they observed a considerable amount of toxicity, short runs of ventricular tachycardia in about 50 per cent of their patients.

DR. GOLD: That is exactly what I would think would happen. If the fractions are too close together, the total dose of 1 mg. of ouabain will cause a good deal of toxicity. If the fractions are smaller and the intervals longer, which should be the practice in the interest of safety, it is found that many patients will require as much as 1 mg. total to induce the full effects.

DR. MODELL: I wonder if we might not draw the conclusion from this discussion that the caution which has been suggested of dividing the 3 or 4 cat unit dose of digitoxin into fractions given at intervals is really not necessary, since it seems to be safe to give as much as 5 cat units of a digitalis material like ouabain at one time by the intravenous route without toxicity.

DR. GOLD: Dr. Luckey, perhaps you will try your hand at that question. Why do you recommend splitting up the digitalizing dose of digitoxin and giving only 0.8 mg. at the start?

DR. LUCKEY: I think that in that way we protect the 2 or 3 per cent of the patients who vomit from the single dose of 1.2 mg. I believe that it is a mistake to think of digitalis intoxication as merely a matter of nausea and vomiting. During poisoning something more basic is also going on which is associated with a decreased efficiency of the myocardium. Would you care to comment on that?

DR. GOLD: I am not quite sure what that means. I was not aware that anything of consequence happens when the dose of a digitalis material oversteps the bounds a little bit and causes nausea or vomiting. It is very disturbing indeed when the overdosage is extreme. Your point is well taken, however, and I agree that it is well to guard against making people sick with digitalis if you can avoid it. I would question whether you can avoid it completely. I am inclined to doubt that starting digitoxin therapy with 0.8 mg. and following it with 0.4 mg. in six hours materially reduces the incidence of toxicity. It lengthens out somewhat the course of digitalization but in the case of a material like digitoxin which develops its action rather slowly, I would venture the guess that you end up with about the same incidence of nausea or vomiting. I have been very much struck by the reports in the literature which rejected my suggestion for the use of 1.2 mg. at one time in initial digitalization and then presented accounts of toxicity in which that amount was given in divided doses. I think it is important for us to fix in mind the fact that the most effective digitalis therapy is impossible without some incidence of toxicity. There is involved here a basic law relating to variability in individual responses. If you insist on a method of dosage which yields no minor toxicity, you sacrifice therapeutic efficiency. One might put it in this way: the best dosage of a drug is one which yields the highest incidence of therapeutic results, not without toxicity but with a reasonably low incidence of minor toxicity. I doubt that any good method of digitalization has ever been devised which in its application to large groups of patients will show less than about 1 or 2 per cent of minor toxic reactions.

DR. JANET TRAVELL: I would like to ask Dr. Gold to say something about some of the other preparations of digitalis besides the two that have been mentioned here, digitoxin and ouabain. Are any of the others worth mentioning?

DR. SEYMOUR RINZLER: I would like to extend that question. Dr. De Graff and his collaborators have said a good deal about advantages in the matter of rapid excretion and greater margin of safety between the therapeutic and toxic dose for some of the other preparations. How real are these things?

DR. GOLD: Perhaps Dr. LaDue would like to comment on these points.

DR. LADUE: I believe there is a difference between digitalis preparations in regard to the range between the therapeutic and toxic dose. This range is smaller with some and larger with others. We were led to this possibility by the experiments of Visscher at the University of Minnesota in which he showed with the heart-lung preparation that there were very marked differences in the range between therapeutic and toxic doses for different members of the lanatoside series. We then looked into this matter in the treatment of patients and found that lanatoside C produced much less toxicity than ouabain or digitoxin in what seemed to be comparable doses in terms of cat units.

DR. GOLD: In answer to Dr. Travell's question concerning other materials of the digitalis group, I might say a few words about cedilanid® or lanatoside C and digoxin.® These two materials have a shorter duration of action than digitoxin. It is in some patients possible to repeat a nearly full digitalizing dose every second or third day without cumulative effects. Much has been made of this fact as a supposed advantage over digitoxin, the action of which lasts longer, and attention has been focused in this connection entirely on the problem of overdigitalization. It is probably an advantage in the most careless kind of overdigitalization. The other side of this picture has not received the attention it deserves, namely, how uniform is the course of digitalis maintenance with preparations that are very rapidly excreted. A lapse of two or three days in the dosage of digitoxin would not seriously upset the level of maintenance, while in many cases such a lapse with cedilanid or digoxin calls for redigitalization. In the very unstable case of auricular fibrillation, the rapidly eliminated materials like cedilanid and digoxin sometimes present some difficulty in maintaining a smooth course. Whether one considers the rapid excretion as an advantage or a disadvantage, therefore, depends on the point of view. I am inclined to regard it as a disadvantage on the whole. There has been a kind of scare thrown into the subject of digitoxin therapy in statements regarding an alleged inordinately long duration of poisoning. The fact remains that the patient who develops nausea or vomiting with digitoxin recovers from it in a day or so in the vast majority of instances. This is indistinguishable from the picture of overdigitalization that we are all familiar with in the case of digitalis leaf which is still in many quarters a favored preparation.

I see that Dr. LaDue believes cedilanid has a wider margin of safety than ouabain or digitoxin. I might call attention to the fact that in a recent report Batterman and DeGraff presented some figures showing that the margin of safety is essentially the same for cedilanid, digoxin, digitoxin and digitalis, but about 40 per cent greater in the case of amorphous gitalin which they now advocate as the preparation of choice. I presume, Dr. Rinzler, that your question has this report in mind. I recently had an opportunity to discuss this very matter as a member of a panel at the meeting of the American College of Physicians in Atlantic City. I do not believe they have established their point. Their data show differences in dosage as high as 700 per cent between the most susceptible and the most tolerant patients I strongly suspect that a difference of 40 per cent in averages based on such a wide range of dosage would turn out to be a chance occurrence if the figures were subjected to statistical analysis. The notion of a greater "margin of safety" has great appeal, since every doctor would prefer to use the safer preparation, the one with the larger margin of safety. There have been many attempts to establish differences in the margin of safety for preparations of digitalis but none has proved successful. The work of Visscher, which was mentioned by Dr. LaDue, showing differences in the margin of safety in heart-lung preparations of the dog has not been confirmed. Dr. Cattell and I showed that the same question receives different answers depending on the method for ascertaining the margin of safety. There are many technical difficulties in the way of establishing differences in the margin of safety and an entirely satisfactory technic for this purpose has never been devised. Beware of any claim for greater margin of safety. The method is full of pitfalls. The most prominent obstacle to a reliable comparison of margins of safety in man is the technical difficulty of establishing with precision the minimal therapeutic and minimal toxic dose because of the numerous factors which can throw off both of these values in an actual determination.

DR. FRANK FERGUSON: What do you use routinely for rapid digitalization?

DR. LADUE: I give 1.6 mg. of lanatoside C intravenously at one time, taking three to five minutes for the injection. This method is especially useful in the attempt to terminate a paroxysm of auricular tachycardia. We have found it more successful than the method by which the dose is divided and fractions given at intervals of two hours. Transient nausea and vomiting occurs in about 8 per cent of the patients when the drug is given in this way but we have seen no serious toxicity.

DR. LUCKEY: I heard others refer to this statement of Dr. LaDue to the effect that the margin of safety is greater for lanatoside C than for other materials. I am not impressed with the evidence. In the studies with heart-lung preparations an expression of margin of safety was obtained by relating the therapeutic effect in the heart-lung preparation with the dose required to kill the intact animal. I would question

whether such a ratio would have much meaning in application to man.

DR. GOLD: I agree with Dr. Luckey. There is no satisfactory evidence for the position that the margin of safety is materially different for the various members of the digitalis group. If there is any difference, I suspect it is much too small to reveal itself in the clinical use of the drugs.

DR. READER: I have two questions. Do you use the electrocardiogram routinely for the control of digitalization? Is it not true that a patient on a maintenance dose of digitoxin may go on for months without trouble and then develop minor toxic effects?

DR. LUCKEY: In regard to your point about digitoxin, toxic effects will of course appear if the maintenance dose is somewhat too large and exceeds in the particular individual the rate of excretion, but this applies to digitalis as well.

DR. READER: I did not mean to imply that digitoxin was different from digitalis in this respect but merely to emphasize that after many months of maintenance minor toxic effects may occur with the digitalis materials.

DR. GOLD: I am glad Dr. Luckey made the point in regard to delayed toxic effects during maintenance that digitoxin is no different from digitalis. He mentioned the possibility that in a particular person what is believed to be the true maintenance dose turns out in the course of time to have been too large and to have produced cumulative effects. There are other factors responsible for the late emergence of a minor toxic effect during so-called maintenance. Patients undoubtedly show marked fluctuations in their susceptibility to digitalis preparations during a period of months and the appearance of a minor toxic effect may be due to these factors in some instances rather than to cumulative effects. In the course of some of our studies we have had occasion to continue a particular dose of digitalis or digitoxin after the appearance of nausea, and in some cases even vomiting, when we had reason to suspect that some other factor was responsible for the vomiting, and we were quite surprised to find how often the nausea and vomiting subsided even while the drug was continued. This might indicate the development of a tolerance but I suspect that in the majority of cases it simply means that the nausea and vomiting were due to some factor other than the digitalis or some transient factor which made the patient unduly susceptible to a level of digitalization which was well below the toxic level most of the time.

DR. READER: How about my question regarding the electrocardiographic control of digitalization?

DR. LUCKEY: We do not use it routinely. The fact is that in most of these cardiac patients we have repeated electrocardiograms which supply information concerning toxic effects on the heart. When we become uncertain regarding irregular rhythms which might be premature contractions due to the drug, we take additional electrocardiograms to establish the position. In some situations, however, the electrocardiogram can be quite helpful in following the course of digitalis medication.

DR. FERGUSON: It is not quite clear to me whether it is your opinion that, among the rapidly acting digitalis materials, one is better than another. Is one preferable to another or are they all about the same?

DR. LUCKEY: I think there is not much to choose between them. Use the one with which you have become familiar.

DR. GOLD: There is the point that ouabain is the only preparation among the group of rapidly acting materials which is non-proprietary.

DR. MODELL: Would it be worth saying a word about acetyl-strophanthidin, which is far more rapidly acting than ouabain?

DR. GOLD: This is a very interesting preparation. The acetyl ester of strophanthidin is a partial synthetic with a digitalis-like action on the heart which develops after intravenous injection with almost the speed of epinephrine. By the time the injection is finished, about five minutes, more than half of the effect of the dose has already appeared and within about ten to fifteen minutes the effect is fully developed. It wears off in four or five hours. There should be uses for a material of this kind in, for example, acute pulmonary edema in which heroic measures may be necessary The rapid onset is of obvious advantage but the rapid disappearance of the effect is also of advantage because in such situations requiring full rapid dosage there is great risk of overrunning and producing toxic effects. If that has to happen, it is well to have it occur with a preparation which wears off so quickly. Of course, after the presenting threat to the patient from the pulmonary edema is brought under control one can proceed to continue the digitalization with other materials.

It ought to be of considerable interest in connection with the attempts to abolish auricular paroxysmal tachycardia. We have been accustomed to thinking of ouabain as a very rapidly acting glycoside but it is very slow by comparison with acetyl-strophanthidin. It takes from one to two hours for ouabain to develop its full effects after intravenous injection, as against about fifteen minutes for this compound. Have you had occasion to use it, Dr. Luckey?

DR. LUCKEY: We have had very little experience with it. I think there has been a recent report to the effect that it is unduly difficult to control dosage. Is that incorrect?

DR. GOLD: I think you refer to a recent report in which there was a good deal of toxicity of acetyl-strophanthidin but if you will examine it you will see that the doses were simply too large. That is the sort of thing that has given ouabain such a bad reputation for toxicity, excessive dosage. Dr. Modell, you might say a word about the dosage of acetyl-strophanthidin.

DR. MODELL: Acetyl-strophanthidin is one-half as potent as ouabain, and we found that 1 mg. produced the same effect as 0.5 mg. of ouabain. If one gives 0.5 mg. intravenously as the first dose and 0.25 mg. every ten minutes until the desired concentration is built up to produce the effect one is after, one should encounter very little toxicity.

DR. GOLD: Our time is about up. I had the thought that a conference on the choice of a digitalis preparation would be marked by sharper controversy than has appeared in this conference. The literature gives one every reason for suspecting that opinions differ widely. You might be interested in knowing the estimate that more than one-half of all prescriptions written for any digitalis material in the United States today call for digitoxin.

SUMMARY

DR. GOLD: The perennial problem of the choice of a digitalis preparation and its most effective use was explored in the conference today in relation to current preparations and diversified experience. Digitoxin, digoxin, cedilanid, ouabain, gitalin, acetyl-strophanthidin received attention from the standpoint of particular indications, dosage and method of administration. Is a slowly or a rapidly eliminated digitalis material preferable for routine digitalization? Is there any advantage in dividing the 1.2 mg. dose of digitoxin into fractions? Is there any difference in the margin of safety among different members of the digitalis group? Do patients in advanced congestive failure require larger doses than those in mild failure? What is the meaning of the reported experience that a large dose of cedilanid may be given to a digitalized patient without toxicity? Does it require more units of any one digitalis material than of any other to produce similar effects by intravenous injection? These are some of the propositions involving much debated questions which were subjected to analysis, criticized or defended in this conference. Times have changed. Digitalis leaf and the tincture were not even mentioned here. When we were medical students, and for some years thereafter, the crude leaf and its galenicals were the preparations of choice. There seems to be no doubt from the discussion that for most purposes digitoxin has taken their place.

Clinico-pathologic Conference

Amyloidosis of the Liver and Cardiac Failure

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. J. (No. 12016), was a white married contractor, fifty years of age, who was admitted to the Barnes Hospital for the first time on March 11, 1947, when he was forty-four years old. He stated that he had worked excessively long hours for the previous ten years, and that during this period his habits were of necessity irregular. After eating large meals he occasionally experienced right lower quadrant pain lasting ten to fifteen minutes, often relieved by the passage of gas. For two years he had noted that his stools were blood-streaked and had attributed the bleeding to hemorrhoids. For about the same length of time he had had slight difficulty in initiating urination.

At the time of admission physical examination revealed his temperature to be 36.8°c., pulse 75, respirations 15 and blood pressure 133/90. The positive findings included moderate obesity, a maculopapular rash over the upper chest and shoulders, slight arteriolar narrowing in the fundi, a protruberant abdomen and a palpable liver edge 3 cm. below the costal margin. Otherwise physical examination was within normal limits.

Laboratory data were as follows: blood count: red cells, 5,360,000; hemoglobin, 16.5 gm. per cent; white cells, 7,050; differential: 1 per cent basophils, 5 per cent non-segmented neutrophils, 66 per cent segmented neutrophils, 37 per cent lymphocytes and 1 per cent monocytes. Urinalysis: specific gravity, Q.N.S.; protein, negative; sugar, negative; sediment, 2 to 4 white blood cells per high power field. Blood Kahn test, negative. Basal metabolic rate, +3 per cent, +1 per cent. Electrocardiogram: indeterminate. A complete gastrointestinal series, including cholecystogram, was within normal limits.

The patient remained in the hospital only three days and was discharged on March 15, 1947.

For the three years following discharge he continued to note occasional blood streaking of his stools at intervals of three to six months. He had no associated pain and denied anorexia, nausea, vomiting, abdominal discomfort, constipation or diarrhea. When admitted for the second time on September 18, 1950, his only other complaint was occasional bloating.

On this occasion physical examination revealed the temperature to be 37.4°c.; pulse, 80; respirations, 16 and blood pressure 120/90. A few scattered hyperkeratotic lesions were present over the skin of the back. Cardiac examination was completely negative. The liver edge was palpable at the costal margin. On rectal examination a large, firm, presumably thrombosed internal hemorrhoid was felt. The prostate was two to three times enlarged, soft and non-tender. The remainder of the examination was within normal limits.

The laboratory data included the following: hemogram, normal; urinalysis: specific gravity, 1.027; protein, negative; sugar, negative; sediment, 3 to 10 white blood cells per high power field. Stool guaiac: faintly positive. Blood cardiolipin: negative. Blood chemistry: non-protein nitrogen, 20 mg. per cent; fasting blood sugar, 76 mg. per cent. Gastrointestinal series: negative. Electrocardiogram: "abnormal form of ventricular complex."

While in the hospital the patient had a proctoscopic examination which was negative. He was discharged on September 21, 1950.

After leaving the hospital he was well until July, 1952, when he began to note dyspnea on exertion. He had been unsuccessful in his attempt to lose weight by dieting and consulted his physician in August, 1952, at which time he was found to have albuminuria. He was given ammonium chloride and had a good diuresis with relief of dyspnea. He was then maintained

on a low sodium diet and did well until two weeks prior to his third admission when, following dietary indiscretions and an increase in alcoholic intake, he again began to have dyspnea on exertion and an increase in the size of his abdomen. Eight days prior to entry he again was seen by his physician, was given ammonium chloride and was advised to reënter the hospital. The ammonium chloride promoted an effective diuresis so that the patient had lost 12 pounds by the time he was admitted on October 25, 1952.

Physical examination revealed the temperature to be 36.7°C.; pulse, 78; respirations, 14 and blood pressure 130/75. The pertinent physical findings were as follows: the lungs were clear to percussion and auscultation. Examination of the heart revealed the maximal cardiac impulse in the mid-clavicular line in the fifth interspace. The sounds were of good quality but P_2 was louder than A_2. A grade two blowing apical systolic murmur was audible. The abdomen was obese, soft and non-tender. The liver edge was palpable 6 cm. below the right costal margin and was non-tender. The prostate was enlarged approximately three times normal and was tender. There was no edema and the neurologic examination was negative.

The laboratory data were as follows: blood count: red cells, 4,780,000; hemoglobin, 15.7 gm. per cent; white cells, 7,850; differential: 1 per cent basophils, 4 per cent eosinophils, 3 per cent non-segmented neutrophils, 29 per cent lymphocytes and 15 per cent monocytes. The platelets and red blood cells appeared normal. Urinalysis: specific gravity, 1.017; protein, 4+; sugar, negative; microscopic, occasional white blood cell; culture: few colonies of Staphylococcus albus. Blood chemistry: non-protein nitrogen, 23 mg. per cent; cholesterol, 140 mg. per cent; cephalin-cholesterol flocculation test, negative; thymol turbidity test, 0.4 units; total protein, 5.8 gm. per cent; albumin, 4.3 gm. per cent; globulin, 1.5 gm. per cent; alkaline phosphatase, 3 Bodansky units. Venous pressure: 210 mm. of water. Circulation time (decholin): thirty-two seconds. Basal metabolic rate: +11 per cent, +7 per cent. Roentgenogram of the chest: cardiac enlargement predominantly left ventricular; ? pulmonary congestion. Intravenous pyelograms: negative for the right kidney, grossly normal for the left kidney, indeterminate for anatomic detail. Electrocardiogram: abnormal form of ventricular complex; ? posterolateral myocardial injury.

On admission the patient was given a low salt diet and was digitalized. During the ten days in which he remained in the hospital he lost 13 pounds. A urine concentration test was performed with the maximum value recorded 1.019. Tests for orthostatic albuminuria showed 1+ protein when the patient was at rest, 2+ after he was up and about. Two PSP tests were performed. On the first the patient excreted only 7.5 per cent of the dye in fifteen minutes, but on the second there was 40 per cent excretion in fifteen minutes and a total of 75 per cent in two hours. He left the hospital on November 4, 1952, and was advised to continue digitalis and the low salt diet.

On the prescribed regimen, plus ammonium chloride intermittently, the patient did quite well until one month prior to his fourth admission when he developed chills, fever and a cough productive of rusty sputum. He was treated with oxytetracycline and his symptoms abated over a ten-day period. Three weeks prior to admission, however, his fever returned and a week thereafter an x-ray film was obtained which showed an infiltration at the right lung base. The patient continued ambulatory but because his weight increased and he became progressively dyspneic, he was admitted on January 22, 1953.

Physical examination revealed the temperature to be 36.3°C.; pulse, 80; respirations, 20 and blood pressure 134/80. Positive physical findings included dullness to percussion, absent vocal fremitus, distant breath sounds and a few rales at the right base. The maximal cardiac impulse was in the fifth intercostal space, 13 cm. from the mid-sternal line. The rhythm was regular and P was greater than A_2. A grade two systolic murmur was again heard at the apex. One observer described a grade one systolic murmur over the aortic area and a soft diastolic murmur along the left sternal border, the latter confirmed by several other examiners. The liver edge was palpable 6 cm. below the right costal margin and the splenic tip was felt 2 cm. below the left costal margin. Rectal examination revealed a hemorrhoidal tag and enlargement of the prostate as before. The neurologic examination was negative.

The laboratory data were as follows: blood count: red cells, 4,600,000; hemoglobin, 14.3 gm. per cent; white cells, 7,600; differential: 2 per cent eosinophils, 57 per cent segmented neutrophils, 39 per cent lymphocytes and 2 per cent monocytes. Red blood cells and platelets

appeared normal. Urinalysis: specific gravity, 1.016; protein, 2+; sugar, negative; sediment, 5 to 8 white blood cells per high power field; Bence-Jones protein: negative; total twenty-four-hour protein excretion, 1.4 gm. per L. Stool guaiac: negative. Blood chemistry: non-protein nitrogen, 15 mg. per cent; sodium, 151.2 mEq./L.; potassium, 4.9 mEq./L.; carbon dioxide combining-power, 34.4 mEq./L.; chloride, 99.1 mEq./L.; cephalin-cholesterol flocculation test, negative; thymol turbidity test, 1.6 units; total protein, 6.2 gm. per cent; albumin, 4.2 gm. per cent; globulin, 2.1 gm. per cent; alkaline phosphatase, 3.7 Bodansky units; cholesterol, 108 mg. per cent; prothrombin time, 50 per cent of normal; total bilirubin, 1.39 mg. per cent; sodium bilirubinate, 0.31 mg. per cent; bilirubinglobin, 1.08 mg. per cent. Venous pressure: 180 mm. of saline. Circulation time (decholin): twenty seconds. Bromsulfalein retention: 46 per cent at thirty minutes. Roentgenogram of the chest: right pleural effusion; cardiac enlargement, predominantly left ventricular; ? pulmonary congestion. Electrocardiogram: as before.

Shortly after admission thoracentesis was performed and 600 cc. of clear yellow, slightly turbid fluid were removed from the right chest. A roentgenogram obtained immediately after this procedure revealed only a slight decrease in the amount of pleural fluid. The patient was subjected to bronchoscopy and no abnormalities were noted. Bronchial washings and one specimen of sputum were negative for acid-fast organisms. A quantitative bromsulfalein test was interpreted as being "compatible with severe vascular disease of the liver." A liver biopsy was performed and a diagnosis of amyloidosis was made by the surgical pathologist. On the fifth hospital day fluid was again removed from the right pleural cavity, a total of 860 cc. of turbid reddish-yellow fluid being obtained. The fluid had a specific gravity of 1.015 and contained 2.1 gm. per cent of protein. The patient was maintained on digitalis and a low salt diet and lost 12 pounds. When the diagnosis of amyloidosis of the liver was reported, the patient was begun on cortisone. Within one week he regained 3 pounds, but subjectively he was markedly improved. The pleural fluid became minimal and he was discharged from the hospital on February 17, 1953.

After he left the hospital the patient continued both digitalis and cortisone. His edema persisted and was only partially controlled by ammonium chloride and mercurial diuretics. His weight varied between 163 and 170 pounds. Although he was dyspneic on exertion, and on one or two occasions was troubled by paroxysmal nocturnal dyspnea, he denied chest pain, fever or cough. His only other complaint was upper abdominal discomfort after eating. He entered the Barnes Hospital for the last time on December 19, 1953.

Physical examination revealed his temperature to be 36.8°C., pulse 88, respirations 22 and blood pressure 120/80. The patient was obese and appeared chronically ill. Examination of the head, eyes, ears, nose and throat was within normal limits. There was dullness to percusion, decrease in fremitus and diminished breath sounds over the lower half of the right chest posteriorly, and fine moist rales were heard over the left base. Cardiac dullness extended 11 cm. from the mid-sternal line in the fifth left interspace. Heart sounds were of good quality, the rhythm regular, and no murmurs were heard. The liver edge was felt 6 cm. below the right costal margin and extended across the epigastrium. The splenic edge was palpable 6 cm. below the left costal margin. The testes were described as enlarged, firm and non-tender. Rectal examination revealed the prostate to be smooth, firm and about twice normal size. There was 3+ pretibial edema and 1+ sacral edema. Neurologic examination was within normal limits.

Laboratory data were as follows: blood count: red cells, 5,400,000; hemoglobin, 15 gm. per cent; white cells, 7,600; differential: 2 per cent non-segmented neutrophils, 65 per cent segmented neutrophils, 28 per cent lymphocytes, 5 per cent monocytes. The platelets appeared adequate and the red blood cells normal. Urinalysis: specific gravity, 1.010; protein, 4+; sugar, negative; sediment, 1 to 5 white blood cells, 2 to 3 red blood cells, occasional granular cast and 1 to 2 hyaline casts per high power field. Stool guaiac: negative. Blood chemistry: non-protein nitrogen, 49 mg. per cent; sodium, 140.9 mEq./L.; potassium, 4.2 mEq./L.; carbon dioxide combining-power, 32.1 mEq./L.; chloride, 108 mEq./L.; total protein, 5.5 gm. per cent; albumin, 3.5 gm. per cent; globulin, 2.0 gm. per cent; cholesterol, 190 mg. per cent; cephalin-cholesterol flocculation, negative; thymol turbidity test, 0.5 units; alkaline phosphatase, 6.9 per cent; total bilirubin, 3.60 mg. per

cent; sodium bilirubinate, 1.38 mg. per cent; bilirubinglobin, 2.22 mg. per cent. Roentgenogram of the chest: generalized cardiac enlargement, predominantly left ventricular; right pleural effusion; pulmonary vascular congestion. Electrocardiogram: abnormal form of ventricular complex.

On admission the patient was continued on a low salt diet and digitalis but cortisone was stopped. Ammonium chloride and mercurial diuretics were used repeatedly with significant diuretic response. From December 22nd until December 30th pleural fluid was removed on ten occasions; on each of two days it was withdrawn twice. Each time 450 to 1,000 cc of straw-colored fluid were obtained, and the total volume in the ten-day period was 7,750 cc.

On the fifth hospital day, shortly after a thoracentesis, the patient's blood pressure dropped to 90/60 but soon returned to normal. The non-protein nitrogen on that day was 37 mg. per cent. On the eighth hospital day the patient was noted to be having more frequent episodes of dyspnea and a gallop rhythm was audible. The dyspnea was improved after administration of aminophyllin by rectal suppository. On the eighth hospital day the serum sodium was 128.6 mEq./L. On the eleventh hospital day the patient's respirations were labored, despite the fact that his weight had decreased from 166 to 155 pounds. On the thirteenth hospital day he had a mild febrile reaction following the injection intramuscularly of a preparation of liver extract. The following day, January 1, 1954, he suddenly became cyanotic and his respirations were noted to be gasping. A house officer saw him immediately and was unable to palpate the pulse. A few generalized convulsive movements occurred and the patient died.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: If the clinical diagnosis made in this case was correct this man suffered from a disease which has until recently been considered to be rare, there being only about seventy-five or eighty cases reported in the literature. It is a disease, however, that has attracted increasing interest, particularly on the part of cardiologists, so that a growing number of examples are being recognized.

In respect to the present patient the natural history of the disease is unusually well documented. When he was first admitted to the Barnes Hospital in 1947 at the age of forty-four, there were no cardiac symptoms and the cardiovascular system was normal on physical examination. A negative cardiac examination was also recorded on the patient's second admission in 1950, although on that occasion the electrocardiogram was interpreted as showing an "abnormal form of ventricular complex." On this basis one may perhaps assume that the disease had begun to be manifested by 1950, but the first recognized symptoms presumably attributable to cardiac amyloidosis—dyspnea and edema—developed in July 1952, approximately eighteen months prior to the patient's death. He was admitted to the hospital at which time his blood pressure was normal, but the heart was enlarged. No murmurs were audible. The liver was increased in size and proteinuria was present. Hepatic and renal function, as measured by the usual tests, was not impaired.

The patient was treated for cardiac failure and improved, only to be admitted two months later presumably for unresolved pneumonia and right pleural effusion. On that occasion an aortic diastolic murmur was described by a number of observers but subsequently it was not heard again. On the fourth admission the liver was again noted to be enlarged and for the first time splenomegaly was described. Altered liver function was indicated by abnormal bromsulfalein retention. Treatment for cardiac failure was again prescribed and several thoracenteses were performed; the patient improved and the pleural fluid did not recur. Dr. Harold Joseph, who was then assistant resident on the medical service, deserves credit for first suspecting amyloidosis. It was at his insistence that a punch biopsy of the liver was done, and histopathologic confirmation of the clinical diagnosis of amyloidosis obtained. Treatment with cortisone was instituted and continued until the final admission ten months later.

The patient required frequent diuretic injections in order to control his edema and it was because of persistent symptoms of cardiac failure that he was admitted for the fifth and last time in December, 1953. The findings then included cardiac enlargement, bilateral pleural effusions, hepatosplenomegaly and peripheral edema. It is pertinent that the tongue was never enlarged and the skin and mucous membranes were essentially normal in appearance. One observer described the testes as enlarged. The patient died about 2 weeks after admission; his course is

described in the protocol. A large number of thoracenteses was performed but the pleural fluid reaccumulated with alarming rapidity. Because the patient developed weakness and hypotension it was planned to evaluate adrenal cortical function, and procedures designed to do so were underway when he suddenly expired. Dr. Elliott, would you discuss the radiologic findings?

DR. GLADDEN V. ELLIOTT: This patient had numerous radiographic examinations prior to his death; included were a number of gastrointestinal series and cholecystograms, all of which were interpreted as normal. I have reviewed them and find no reason to differ with the previous interpretation. Similarly, intravenous pyelograms done in October, 1950, showed no detectable abnormality. The significant radiologic findings were those related to the chest examination. Our first chest film was made on the third admission in late 1952. At that time there was marked cardiac enlargement, involving chiefly the left ventricle. There was also some suggestion of vascular congestion but no other changes from the normal. In January, 1953, after the patient had developed signs of a right pleural effusion, a film demonstrated that there was a considerable amount of fluid present. After several thoracenteses, a distinct decrease in the size of the pleural effusion was noted. Just before the patient was discharged from the hospital on that admission another chest film showed persistent evidence of pulmonary congestion and cardiac enlargement. The last films were made on the patient's final admission in December, 1953, at which time pleural effusions were again present, particularly marked on the right. We found it difficult to make any comment on the relative size of the heart because of the amount of fluid but it was our impression that the cardiac size had increased somewhat.

DR. SCOTT: There are several points which I think our discussion should cover: first, the establishment of the primary diagnosis of amyloidosis; second, the events of the clinical course during the final admission; and third, the sudden cause of death. Before we ask the pathologists to demonstrate the biopsy specimen upon which the diagnosis was made, it may be profitable to attempt to orient ourselves concerning amyloidosis. Amyloidosis may be classified in a number of ways; in general, the primary and secondary forms are separated. The so-called secondary form, which is associated with some other underlying disease, is the more familiar to most clinicians. Perhaps 80 to 90 per cent of the patients with secondary amyloidosis suffer from tuberculosis, and it is said that the presence of draining sinuses enhances in some way the development of this complication. The remaining 10 to 20 per cent of cases occur in association with pyogenic lesions of the bones such as osteomyelitis or with suppurative diseases of the lung such as abscesses or bronchiectasis. Secondary amyloidosis commonly involves the liver, spleen, kidneys and adrenals.

The second major type—so-called primary or systemic amyloidosis—is characterized by involvement of blood vessels, particularly the small arteries. The organs affected include the heart, muscles, skin and mucous membranes. Rightly or wrongly, under primary systemic amyloidosis there are listed certain "sub-types." Thus 6 to 10 per cent of patients with multiple myeloma are said to show evidence at autopsy of primary amyloidosis. Some authorities express the belief that all patients with multiple myeloma, if they survive long enough, develop primary amyloidosis; the converse point of view is taken by others, namely, that all patients with primary amyloidosis have multiple myeloma. One also finds that so-called primary cardiac amyloidosis is being reported with increasing frequency in the literature. In this form amyloid presumably is almost entirely localized in the heart, although in some of the case reports it is noted that small amounts of the material can be found in the pulmonary and/or the periadrenal vessels. Whether cardiac amyloidosis represents a separate disease or merely a phenomenon of chance distribution is not clear at this time.

Dermatologists describe still another form—lichen amyloidosis—with lesions in the mucous membranes. Again, in these patients amyloid often can be found in the vocal cords, bronchi, stomach and the urinary bladder among other sites, so that there is real reason to question the occurrence of a localized amyloidosis involving the skin alone. In this regard it may be pointed out that in primary systemic amyloidosis, deposits of the material occasionally form localized masses which have been called amyloid tumors.

Dahlin[1] studied fifty-seven cases of primary amyloidosis in which the diagnosis was confirmed pathologically in fifty-four by autopsy. The age range was wide, encompassing patients

[1] DAHLIN, D. C. Primary amyloidosis with report of six cases. *Am. J. Path.*, 25: 105, 1949.

from fifteen to eighty years. The average age was fifty-five, and males and females were approximately equally affected. Forty-six of the fifty-four cases studied at autopsy had cardiac involvement, and in twenty-five amyloid disease of the heart was the primary cause of death. The gastrointestinal tract was involved in thirty-three patients, the tongue in twenty-six. The occurrence of macroglossia is perhaps overemphasized in the clinical literature. The number of patients showing amyloid in other organs in Dahlin's series was as follows: lungs, twenty-four; liver, twenty-one; kidneys, twenty-one; spleen, twenty; muscle, nineteen and skin, thirteen. These data indicate that primary amyloidosis, like the secondary form, affects the liver, spleen and kidneys.

In the series of seventy-one cases of primary amyloidosis reviewed by Higgins and Higgins[2] in 1950, attention was directed to the signs and symptoms presented by the patients. Congestive heart failure with dyspnea and edema occurred in slightly over half the group, and ascites and hydrothorax in one-quarter. Other common findings were generalized muscular weakness in 50 per cent and macroglossia in 40 per cent. Amyloid deposits were noted in the skin and buccal mucosa in 33 per cent and in the lymph nodes in 27 per cent. About 25 per cent had pain in the extremities, one-fifth had some degree of hypertension (above 140/90) and purpura occurred in 15 per cent.

Concerning the problem of differentiation between primary and secondary amyloidosis, it has been suggested that the absence of a specific etiologic factor, minimal involvement of liver, kidneys and spleen and prominent infiltration of the heart, lungs, skin and muscle, atypical staining reactions and occasional appearance of amyloid tumors all point to the primary form. Dahlin,[1] on the other hand, summarizes his views on this subject as follows: "Of all the criteria given for the diagnosis of primary systemic amyloidosis, absence of preëxisting or etiologic disease is the only constant clinical and pathologic finding." In the present case there was no evidence of a preëxisting disease, and according to Dahlin, therefore, it would qualify as an example of primary amyloidosis.

Little is known of the chemical nature of amyloid although the available evidence indicates that it is a protein-carbohydrate complex. It was once thought that the carbohydrate component was chondroitin sulfate, but more recent studies do not support this possibility. Although there appears to be similarity between amyloid and Bence-Jones protein, they are not identical and may be unrelated, even though plasma cells may have a role in the production of amyloid.

FIG. 1. Biopsy of the liver showing a greatly thickened vessel whose wall is infiltrated with amyloid.

Repeated injections of certain substances into mice eventually result in secondary amyloidosis; as in man, the changes are reversible if the inciting agent is eliminated. It is also said that the administration of liver extract is beneficial in secondary amyloidosis in animals and humans. Mice also may develop spontaneously a primary form of amyloid disease; like the analogous situation in man, this entity is uniformly fatal. Dr. Spjut, may we now see the biopsy specimen?

DR. HARLAN J. SPJUT: This section (Fig. 1) was made from tissue obtained by needle biposy. The liver cords are fairly well preserved and there is no real evidence of amyloid disease involving the subendothelial lining of the liver sinusoids. The only changes noted were homogenization of the walls of the small vessels, and special stains showed that in those areas amyloid was present. None was seen in any other site.

DR. SCOTT: The basis for the diagnosis of amyloid disease, therefore, is the very small amounts of the substance present around a few small blood vessels.

DR. SPJUT: That is correct.

DR. SCOTT: Dr. Mendeloff, do you believe that the evidence just presented is sufficient to justify acceptance of the diagnosis of primary amyloidosis?

DR. ALBERT I. MENDELOFF: Yes, it convinces me.

[2] HIGGINS, W. H. and HIGGINS, W. H., JR. Primary amyloidosis—a clinical and pathological study. *Am. J. M. Sc.*, 220: 610, 1950.

DR. SCOTT: In other words, the presence of any amyloid, no matter how minimal, represents a significant abnormality.

DR. MENDELOFF: That is my impression. I do not believe that amyloid is found in the liver except when the disease state exists.

DR. SCOTT: It is quite remarkable that the amount of amyloid may be so minimal. Its presence in the tissues might readily be missed.

DR. CARL G. HARFORD: May I ask what stains are used in the identification of amyloid?

DR. SCOTT: Would you answer Dr. Harford's question, Dr. Thomas?

DR. WILBUR A. THOMAS: There are a number which may be employed—aniline dye derivatives; methyl violet and crystal violet are the ones which we most frequently use in our laboratory, and I believe they are also used by Dr. Ackerman in the surgical pathology laboratory. If the material in question takes one of these stains, we consider the reaction positive. Occasionally the sections are difficult to interpret; but when the abnormal area in the vessel wall is well stained, as was true in this instance, one is on firm ground if he makes the diagnosis of amyloidosis.

DR. SCOTT: Liver biopsy, then, is a useful method in the diagnosis of amyloid disease of the liver. What about the congo red test?

DR. MENDELOFF: Those who have had extensive experience with the congo red tests, particularly Dr. J. Murray Steele[3] and his group in New York, believe that the test, as it has usually been done, is completely unreliable because it is based on a number of erroneous assumptions. Without going into the technical details of the procedure, one of the problems is that in the past a five-minute concentration of congo red in the serum has been taken as the 100 per cent figure, and samples taken fifty-five minutes later have been compared with this original reading. False negative results are obtained because, as Dr. Steele has shown, the disappearance of the dye is rapid in the presence of amyloid disease. By five minutes instead of having a true 100 per cent concentration of congo red circulating there may be less than 50 per cent, the rest having been bound almost immediately in amyloid deposits. One, therefore, is not really comparing the disappearance of dye with its actual concentration at zero time, but with a falsely low initial concentration. Therefore the results may be quite inaccurate. Dr. Steele suggests that the test should be done over a thirty minute period rather than over a sixty-minute one, and that several values should be determined. The results should then be extrapolated on a semilog curve back to 0. Under those circumstances the congo red test may be reliable.

DR. SCOTT: While we are speaking of this type of procedure, will you comment on the quantitative bromsulfalein procedure in this case which you did in your laboratory? The curve was reported as demonstrating severe hepatic vascular impairment although the liver parenchyma, as judged by the specimen obtained by needle biopsy, was quite normal.

DR. MENDELOFF: It is of interest that the quantitative bromsulfalein test should have been so markedly abnormal when other liver function tests were essentially normal a year later. That the test was interpreted as showing chronic vascular disease of the liver merely indicated that the disappearance rate was given by a straight line semilogarithmic curve, implying that there was no defect in the ability of the liver cells to handle the dye but rather that the dye reached the cells in abnormally small quantities. In other words, considerable dye must have been diverted, either because of changes in the vascular architecture of the liver or because the dye did not pass out of the blood vessels in a normal fashion. I think the result is consistent with the pathologic changes in the smaller blood vessels. The curve was like that found in chronic passive congestion of the liver—a slow disappearance rate despite the fact that the hepatic cells were intact and probably could have excreted the dye normally if enough of it had reached them.

DR. LILLIAN RECANT: Is there any evidence that bromsulfalein is taken up by amyloid in the way congo red is?

DR. MENDELOFF: If that were the case, Dr. Recant, one would expect the dye to leave the blood stream promptly just as the congo red does, and the resultant curve would be the opposite to that which was seen here, where the dye remained in the blood for an abnormally long period of time.

DR. SCOTT: Before we leave the problem of the diagnosis of primary amyloid disease, it is pertinent that some clinicians have found

[3] UNGER, P. N., ZUCKERBROD, M., BECK, G. J. and STEELE, J. M. Study of the disappearance of congo red from the blood of non-amyloid subjects and patients with systemic amyloidosis. *J. Clin. Investigation*, 27: 111, 1948.

gingival biopsy to be of value in this regard, even though grossly the tissue appears normal. The procedure is a simple one and probably should be employed when primary amyloidosis is suspected.

To go on with other aspects of the present case, Dr. Harford, would you predict what organs, in addition to the liver, were involved?

DR. HARFORD: The spleen was palpable and may well have been infiltrated with amyloid. The persistence of albuminuria over a number of years suggests that the kidneys, too, were affected. The clinical course clearly points to myocardial involvement; you have already alluded to the fact that adrenal function studies were under way when the patient died, so that I presume the presence of amyloid in the adrenals would not surprise you.

DR. SCOTT: The adrenal is commonly involved in secondary amyloidosis and, in a significant number of patients with primary amyloidosis, there is involvement of the small blood vessels about the adrenal. Before we consider the possibility that the patient had adrenal insufficiency, Dr. Massie, how often in patients with heart failure of obscure etiology is the diagnosis of primary amyloidosis mentioned?

DR. EDWARD MASSIE: It may be considered from time to time but it certainly is relatively rare. The diagnosis has come to my mind on a number of occasions but I cannot recall seeing a patient in whom it was subsequently proven pathologically. In this instance, one's index of suspicion is, of course, high because of the biopsy findings, and since cardiac involvement in primary amyloidosis occurs in a large percentage of patients I would expect that amyloid of the myocardium was responsible for the cardiac signs. There is no other known etiologic factor which seems as likely to me; even though a diastolic murmur was apparently heard by several observers on one admission, it was never heard again and there was no other evidence of valvular disease. The electrocardiographic changes were non-specific and could be attributed to any kind of myocardial infiltration.

DR. SCOTT: All of the layers of the heart may be involved in primary amyloidosis, but the process exhibits a predilection for the endocardium. There have been cases described in which deposition of amyloid in the mitral and aortic valves has been of such proportion that significant valvular defects were produced. The enlargement of the testes, which was described by one observer in this case; suggests that they may have been involved, and although it is noted repeatedly that the tongue was normal it is possible that amyloid deposition in the muscles of the tongue, not apparent on clinical examination, may be found on pathologic examination.

Let us now turn our attention to the treatment of this patient. It will be recalled that cortisone was administered over a long period of time—ten months. There is only limited information in the literature regarding the use of cortisone in amyloidosis, and I have asked Dr. Eisenstein to discuss it.

DR. ALBERT B. EISENSTEIN: First of all, it may be helpful to list some of the substances which in the past have been used experimentally to produce amyloidosis in animals. Among these may be included foreign proteins, antigens of various kinds, killed bacteria, casein, human serum, sulfur and many others. More recently it has been reported that a diet deficient in vitamin C may be associated with the development of amyloidosis.[4] A Danish investigator, Teilum,[5,6] has been able to produce amyloidosis in mice and in rabbits by the use of cortisone and nitrogen mustard although only when either was preceded by injection of sodium caseinate.[3] He has postulated that the mechanism by which cortisone or nitrogen mustard following sodium caseinate results in amyloidosis is that both agents lead to disruption or dissolution of mesenchymal cells *in vivo*, with the formation of amyloid. It is difficult to evaluate these experiments in terms of the human disease, but the observations are certainly of interest and deserve further study.

DR. SCOTT: Dr. Daughaday, have you any information regarding the value of cortisone in patients with amyloidosis?

DR. WILLIAM H. DAUGHADAY: No.

DR. SCOTT: I was able to find one report in which patients with secondary amyloidosis were given liver extract and even though the etiologic factor responsible for amyloidosis persisted, the amount of amyloid present was believed to be

[4] PIRANI, C. L., BLY, C. G., SUTHERLAND, K. and CHERESO, F. Experimental amyloidosis in the guinea pig. *Science*, 110: 145, 1949.

[5] TEILUM, G. Cortisone-ascorbic acid interaction and the pathogenesis of amyloidosis: mechanism of action of cortisone on mesenchymal tissue. *Ann. Rheumat. Dis.*, 11: 119, 1952.

[6] TEILUM, G. Studies on the pathogenesis of amyloidosis. II. Effect of nitrogen mustard in inducing amyloidosis. *J. Lab. & Clin. Med.*, 43: 367, 1949.

reduced significantly.[7] As far as I know this observation has not been confirmed, and there is no evidence regarding the effect of liver extract in primary amyloidosis. Since the latter has been uniformly fatal, perhaps when the diagnosis is made antemortem it would be reasonable to give liver extract in the hope of achieving favorable results. Let us take up now the terminal episode. When the patient was admitted to the hospital for the last time cortisone therapy was discontinued. The problem of the pleural effusions was a serious one, and despite repeated thoracenteses and frequent injections of mercurials fluid reaccumulated rapidly. Then the patient became hypotensive and developed weakness. Dr. Schroeder, do you suppose that these last changes resulted from the low salt syndrome due to excessive removal of pleural fluid or do you suspect that there was involvement of the adrenals by amyloidosis and beginning adrenal insufficiency?

Dr. Henry A. Schroeder: The patient had received cortisone for such a long period of time that significant adrenal suppression certainly occurred. The glands may also have been involved by amyloidosis so that their function on two grounds may well have been seriously impaired. On the other hand, when the patient was admitted adrenal function was presumably within normal limits; at least one would assume so on the basis of normal blood pressure and normal electrolytes. However, the cessation of cortisone therapy may have invoked functional adrenal insufficiency which led to his death.

Dr. Scott: Up to 1950 fifteen cases of Addison's disease due to amyloidosis had been reported.[8] Distinction was not made between the secondary and primary type although presumably most of the cases were due to the former. There is at least one instance, however, in which the primary form of the disease was thought to be responsible.

Finally, as to the terminal event, this patient died rather suddenly and as usual the possibility of coronary occlusion, pulmonary embolism or cardiac arrythmia come to mind as a cause of death. Dr. Massie, can we choose between these on the basis of the available information?

[7] Jacobi, M. and Grayzel, H. Generalized secondary amyloidosis, a clinico-pathological study of 84 cases. *J. Mt. Sinai Hosp.*, 12: 339, 1945–46.

[8] O'Donnell, W. Changing pathogenesis of Addison's disease. *Arch. Int. Med.*, 86: 266, 1950.

Dr. Massie: No.

Dr. Scott: I assume, therefore, that we all agree that this patient had primary systemic amyloidosis with involvement of the myocardium, liver, spleen, kidneys and perhaps the adrenals.

Clinical Diagnosis: Primary systemic amyloidosis; ? adrenal insufficiency.

PATHOLOGIC DISCUSSION

Dr. Wilbur A. Thomas: The lower extremities were moderately edematous and there were 1,200 ml. of clear fluid in the right pleural cavity, 525 in the left and 600 in the peritoneal cavity. The heart was enlarged and weighed 680 gm. (Fig. 2.) It was somewhat dilated but did not have the globular configuration usually described in cases of cardiac amyloidosis. The myocardium was quite firm and rubbery. The color was slightly paler than that of the normal myocardium, and the patterns of muscle bundles appeared to be a little indistinct. The mural endocardium as well as the valvular endocardium was perfectly normal. The coronary arteries showed only a slight amount of arteriosclerosis.

The spleen was enlarged and weighed 450 gm. Its consistency was also quite firm and rubbery. The architectural markings were indistinct, and in the fresh state it had the translucent or glassy appearance associated with amyloidosis. The liver weighed 2,000 gm. It was firm but did not have the rubbery consistency present in the spleen. On the cut surface the architectural markings were fairly distinct and slightly increased, suggesting congestion. The lungs showed some atelectasis and congestion. Each kidney weighed about 300 gm. which is an increase above normal, but they were not otherwise abnormal. In the remaining organs there was no evidence of amyloid or anything else of particular note.

In sections of the heart there is a massive infiltration or deposition of a fibrillary, faintly eosinophilic material which occupies 50 to 60 per cent of the typical microscopic field as shown in Figure 3. Some of the individual muscle fibers are surrounded by this abnormal material and have become atrophic, small and shrunken. The other muscle fibers are about normal in size. They do not show large square nuclei or any other changes suggestive of hypertrophy. In other words, the increase in weight of this

heart from a normal of around 300 to 680 gm. appears to be due entirely to added interstitial material and not to hypertrophy of the myocardium. This is a characteristic finding in cardiac amyloidosis. On staining with methyl violet, at least a portion of the abnormal interstitial substance gave a metachromatic reaction. Much of the substance in these sections, that otherwise appears to be similar, does not stain in this specific manner. This difficulty of staining the amyloid material and other atypical staining reactions are rather characteristic of primary amyloidosis as opposed to secondary amyloidosis in which one ordinarily has no difficulty staining all of the material with the usual stains.

Figure 4 is from a section of the spleen and is typical of the entire organ. There is a tremen-

FIG. 2. The heart showing enlargement and thickening of the myocardium with a typical, firm, glassy appearance. The endocardium and pericardium are not remarkable.

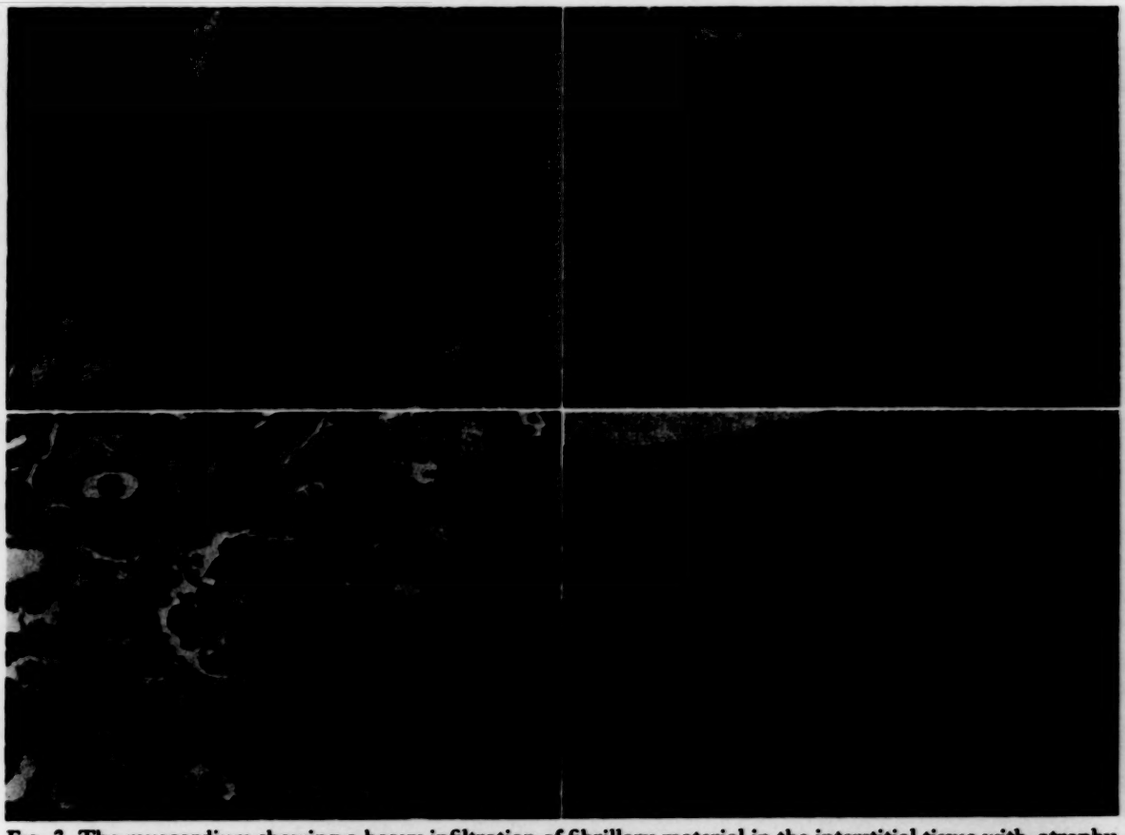

FIG. 3. The myocardium showing a heavy infiltration of fibrillary material in the interstitial tissue with atrophy of some of the surrounded myocardium fibers. This material stained positively for amyloid. The absence of evidence of myocardial hypertrophy is to be noted.

FIG. 4. Spleen with massive infiltration of amyloid in the red pulp and compression of the sinusoids and atrophy of the follicles.

FIG. 5. Amyloid infiltration of the afferent arteriole in the kidney. This vascular infiltration was present throughout the kidneys, and the absence of the deposition of amyloid within the glomerular tuft is in contrast to secondary amyloidosis.

FIG. 6. Adrenal showing massive infiltration of amyloid about the sinusoids in the central portion of the gland.

dous deposition of abnormal material throughout the spleen. Only a few small follicles remain, and the sinusoids are compressed between the columns of amyloid. With methyl violet at least part of this substance, particularly that in the small blood vessels, stains metachromatically. In the kidneys similar material in the small vessels takes the stain quite well. Infiltrated and thickened vessels are present throughout the kidney, and many of the arterioles at the junction with the glomeruli are particularly involved, as illustrated in Figure 5. This is a common feature of amyloidosis and is interesting because hypertension is seen in very few cases of this disease in spite of the presence of these greatly thickened vessels. The glomeruli in the present case show no definite involvement of the glomerular tuft. This is in typical contrast to secondary amyloidosis which involves the glomeruli extensively, in addition to the small blood vessels. Figure 6 shows the adrenal which is the third organ with primary parenchymal involvement as opposed to vascular involvement. The adrenals show rather massive deposition of the same material which also takes the stain for amyloid in much the same fashion as in the other organs. There is only a thin rim of cortical cells remaining about the central mass of perisinusoidal amyloid.

In the liver amyloid was deposited principally in the blood vessels in the manner seen in the biopsy specimen. Vessels throughout the liver were so uniformly involved that a biopsy which included any vessels at all could have been expected to show one that was abnormal. There was none of the perisinusoidal deposition of amyloid often associated with secondary amyloidosis. The liver otherwise showed changes probably due both to congestive failure with central congestion and to the deprivation of blood supply secondary to the extreme involvement of the vessels of the liver. Vascular involvement similar to that in the liver was also present in the pancreas and prostate. Sections of the lung showed congestion and hemosiderin-filled macrophages in the alveoli indicative of cardiac failure.

Thus the anatomic diagnosis is that of primary amyloidosis involving principally the heart, spleen and adrenals and chronic passive congestion of the lungs and liver. The only disturbing feature in considering this primary amyloidosis is the involvement of the parenchyma of the spleen and of the adrenals. Some degree of this parenchymal distribution, usually considered characteristic of secondary amyloidosis, has been noted, however, in a rather large percentage of the reported cases typical of the primary type.

Final Anatomic Diagnoses: Primary amyloidosis of the heart, spleen, adrenals and vessels of the kidneys, liver, pancreas and prostate with cardiomegaly and splenomegaly; chronic passive congestion and edema of the lungs; chronic passive congestion of the liver.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Report

Cerebral Hodgkin's Disease*

Case Report of Hodgkin's Granuloma with Cerebral Invasion

SHERWOOD B. FEIN, M.D. *and* VAUN A. NEWILL, M.D.
Cleveland, Ohio

A REVIEW of the literature reveals that invasion of the brain by Hodgkin's granuloma is extremely rare. Goldman,[4] in a review of 212 cases, found ten cases with involvement of the central nervous system. None, however, showed direct invasion of the brain. The spinal cord was involved in each of these cases. The mode of involvement was epidural invasion by Hodgkin's granuloma which resulted in transverse myelitis due to diminished blood supply. Jackson and Parker[5] state that "there is only one case[6] reported in the literature in which a granulomatous lesion was found in the substance of the cortex" and then they cast doubt upon this case because an "earlier biopsy of an axillary lymph node had shown a small round cell sarcoma, and according to the authors themselves, many of the involved organs failed to show a clear-cut histologic picture." Two other possible cases[2,7] and one questionable case[1] of invasion of the brain have been reported. The following report is a case of Hodgkin's disease with invasion of both cerebral hemispheres.

CASE REPORT

A thirty-four year old white male was first admitted to the Veterans Administration Hospital, Cleveland, Ohio, on January 5, 1953, with the chief complaints of weakness, weight loss and convulsions. The history of the present illness began in December, 1945, at which time he was admitted to a hospital because of lymphadenopathy of one year's duration without systemic symptoms. He had freely movable nodes in his supraclavicular, cervical, axillary and inguinal areas. A chest x-ray showed a large mediastinal mass. A biopsy of the supraclavicular nodes established the diagnosis of Hodgkin's disease. He received repeated courses of x-ray therapy to his chest, axilla, spleen, left kidney and cervical and dorsal spine with good results. He was again admitted to a hospital in October, 1951, following a convulsion during which he dislocated both shoulders. Weight loss, weakness, anorexia and severe pruritus gradually developed without fever, chills or pain during the six months prior to his admission to this hospital. He was admitted to this hospital because he had had several convulsions which lasted for five minutes and were followed by transient periods of unconsciousness. He was incontinent during the convulsive seizures.

Physical examination on the first admission showed a well developed, cachectic, young, white male appearing acutely and chronically ill. His sensorium was clouded and he was drowsy. His vital signs were normal. A large, firm, non-movable mass was present in the scalp to the left of the midline in the frontal area. There was no nuchal rigidity, splenomegaly or hepatomegaly. There were nodules in the left supraclavicular, inguinal, femoral and iliac areas. Neurologic examination revealed unequal pupils, ptosis of the right eyelid, marked bilateral papilledema, hyperactive but equal deep tendon reflexes and increased neuromuscular irritability of both upper extremities.

Laboratory examination revealed a white blood cell count of 44,600 on admission with an increased percentage of polymorphonuclear leukocytes. White blood cell counts varied between 8,000 and 42,000 during the remainder of his hospitalization. He had a moderate normochromic normocytic anemia and normal blood urea nitrogen and electrolyte determinations. The chest x-ray was normal. The skull

* From the Veterans Administration Hospital, Cleveland, Ohio.

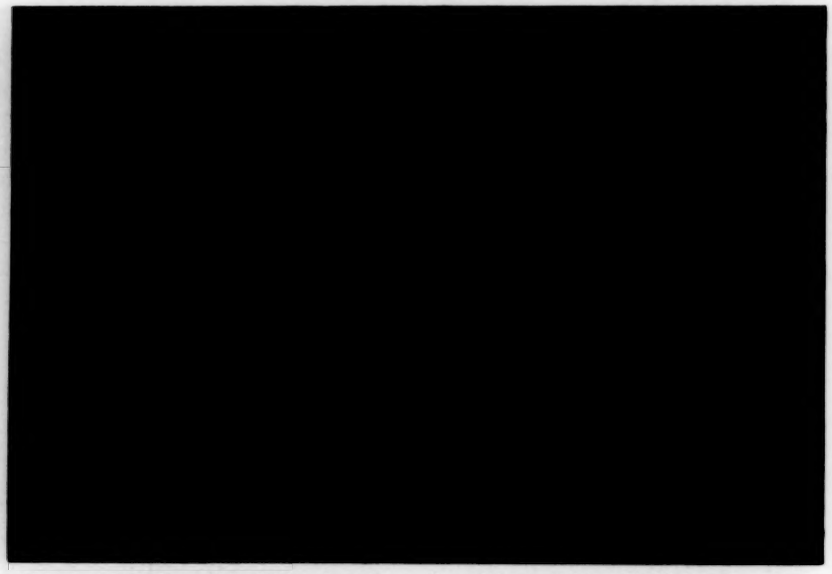

FIG. 1. Hodgkin's granuloma in the frontal lobes of brain.

x-rays showed thickening of the frontal bones anterior to the bregma and erosion of the posterior clinoid processes.

During this hospitalization he had intermittent bouts of fever with lethargy, weight loss and anorexia. A spinal tap was not performed because of marked papilledema which began to subside one month after admission. He had a transient left hemiparesis and right facial weakness. One and again two months after admission he had grand mal seizures followed by right facial weakness, paralysis of the right arm and leg, hyperirritability of the left arm and leg and the presence of a right Babinski reaction. X-ray irradiation to the region of the sella turcica and intravenous nitrogen mustard therapy were followed by moderate resolution of his neurologic findings. Soon he became lethargic, unresponsive and markedly anorexic. At this time a daily dose of 150 mg. of cortisone produced marked improvement. The dosage was gradually reduced to 25 mg. daily, which was continued following his discharge from the hospital on May 13, 1953.

One month later he was readmitted and gave a history of having had a grand mal seizure two weeks previously with residual right paralysis. He had had an increase in anorexia and lethargy during this month.

Physical examination at this time showed a chronically ill, thin, lethargic, relatively unresponsive white male. Neurologic examination revealed ptosis of the right lid, blurring of the optic discs without definite papilledema, an old right facial paralysis, a right hemiparesis, a transient right Babinski reaction, bilateral tremors of his extremities and hyperactive deep tendon reflexes that were more marked on the right. Lymphadenopathy was present in the inguinal, femoral and axillary areas.

Laboratory examination revealed a white blood cell count of 35,000 with 90 per cent polymorphonuclear leukocytes. Again, a moderate normochromic normocytic anemia was present and a work-up for hemolytic anemia was negative. A spinal tap revealed clear, colorless fluid containing 1 lymphocyte per cu. mm., normal sugar and protein and negative cultures for bacteria and fungi. X-ray examination of the chest and skull showed no change from the previous admission.

He had several convulsive seizures during this admission which were controlled by anticonvulsive drugs. Nitrogen mustard therapy did not improve the right hemiparesis but did give symptomatic improvement of his lethargy and anorexia. These symptoms returned rapidly and he became comatose twelve hours prior to his death on July 20, 1953.

Postmortem examination revealed that the patient had Hodgkin's granuloma which had invaded the spleen, lymph nodes (including para-aortic, celiac, axillary, tracheobronchial, bronchopulmonary, anterior mediastinal and mesenteric nodes), bones (including ribs, sternum, vertebrae, frontal bones, sella turcica

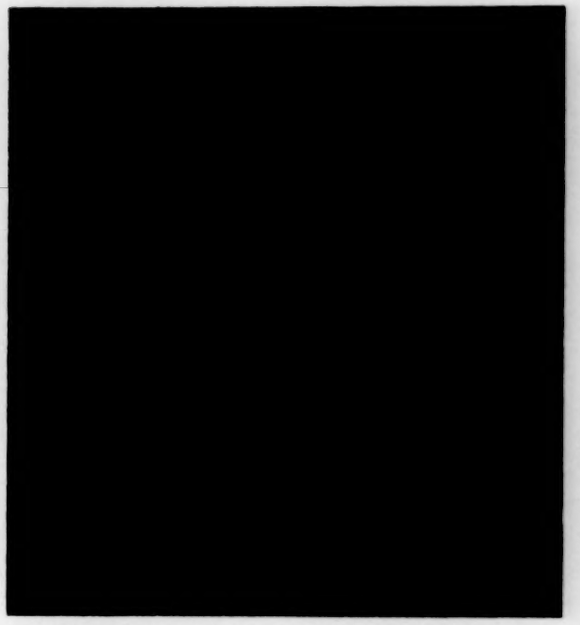

FIG. 2. Brain showing invasion by Hodgkin's granuloma; × 40.

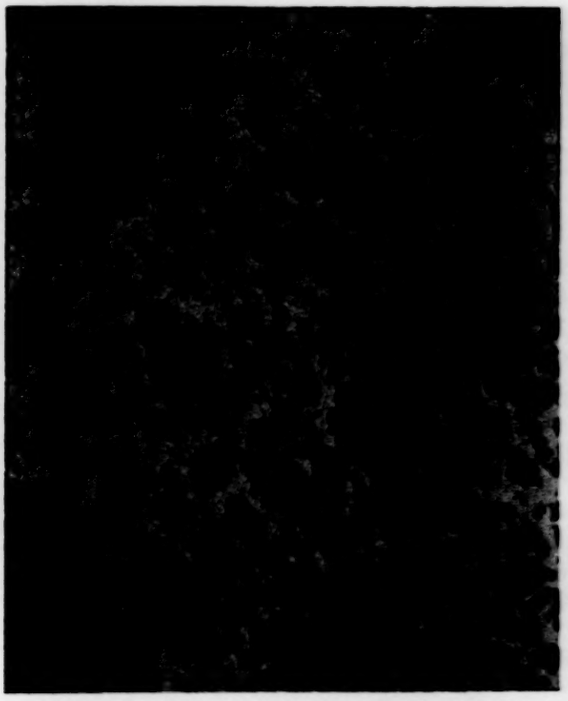

FIG. 2A. Magnification of labelled area on Figure 2 showing lymphocytes, plasma cells, eosinophils, large mononuclear and multinucleated cells consistent with Reed-Sternberg cells and connective tissue from a cellular island of the invading granuloma; × 350.

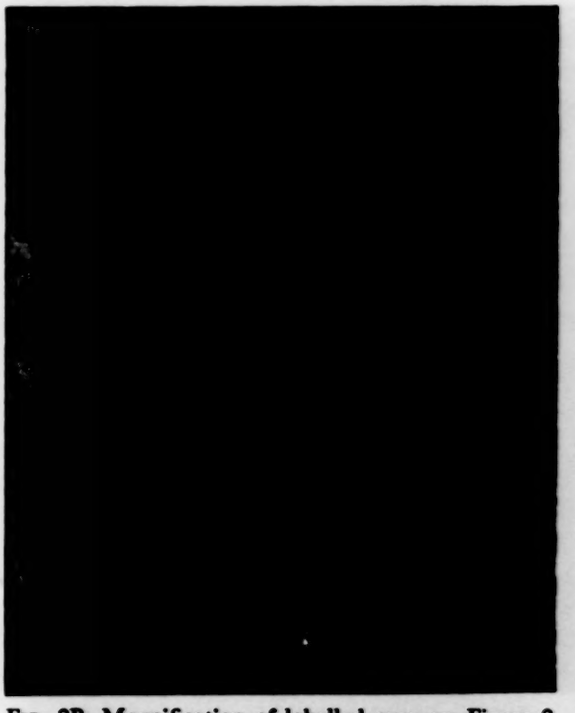

FIG. 2B. Magnification of labelled area on Figure 2 showing Reed-Sternberg cells, connective tissue and a gemistiocyte (A) demonstrating invasion of the tissue of brain; × 400.

and cribiform plate), meninges, cerebrum and focal Hodgkin's infiltration of the liver. He also had chronic pyelonephritis with arterial and arteriolar nephrosclerosis of the left kidney. Atrophy of the spermatogenic cells with aspermia was present, probably as the result of nitrogen mustard therapy. A more detailed description of the skull and brain follows because of their unusual findings.

There was an elevated nodule which was gray with yellow areas of necrosis and which measured 3.5 cm. in width and 3 cm. in length within the skull anterior to the bregma. The nodule involved the inner table of the calvarium in an area that measured 6 cm. in width and 8.5 cm. in length. The dura mater and the sagittal sinus were also invaded by the same mass and the latter was completely obliterated for a distance of 8.5 cm.

The brain weighed 1,550 gm. There was a mass which replaced the left superior frontal gyrus, the middle frontal gyrus, the left cingulate gyrus, the corpus callosum and the superior wall of the left lateral ventricle. (Fig. 1.) The mass also replaced the medial one-third of the right superior frontal and cingulate gyri. It measured 6.7 cm. in the greatest width, was firm, bulging and terminated in the left cingulate sulcus posteriorly. The left lateral ventricle was dilated and contained pale gray gelatinous material. The sagittal sulcus was deviated to the

right and there was compression of the right lateral ventricle.

Microscopic examination revealed that the mass involved the calvarium, meninges and brain, with obliteration of the subdural space. It consisted of interlacing bundles of fibrous connective tissue and many isolated islands of lymphocytes, plasma cells, eosinophils and large mononuclear and multinucleated giant cells consistent with Reed-Sternberg cells. (Figs. 2, A and B.)

SUMMARY

A case of Hodgkin's granuloma with cerebral invasion is reported.

Acknowledgment: The authors wish to thank Dr. Norman P. Shumway, Chief of the Medical Service, and Dr. Joseph R. Kahn, Chief of the Laboratory Service, for their help and criticism of this paper and the Medical Illustrations Department for the illustrations included herein.

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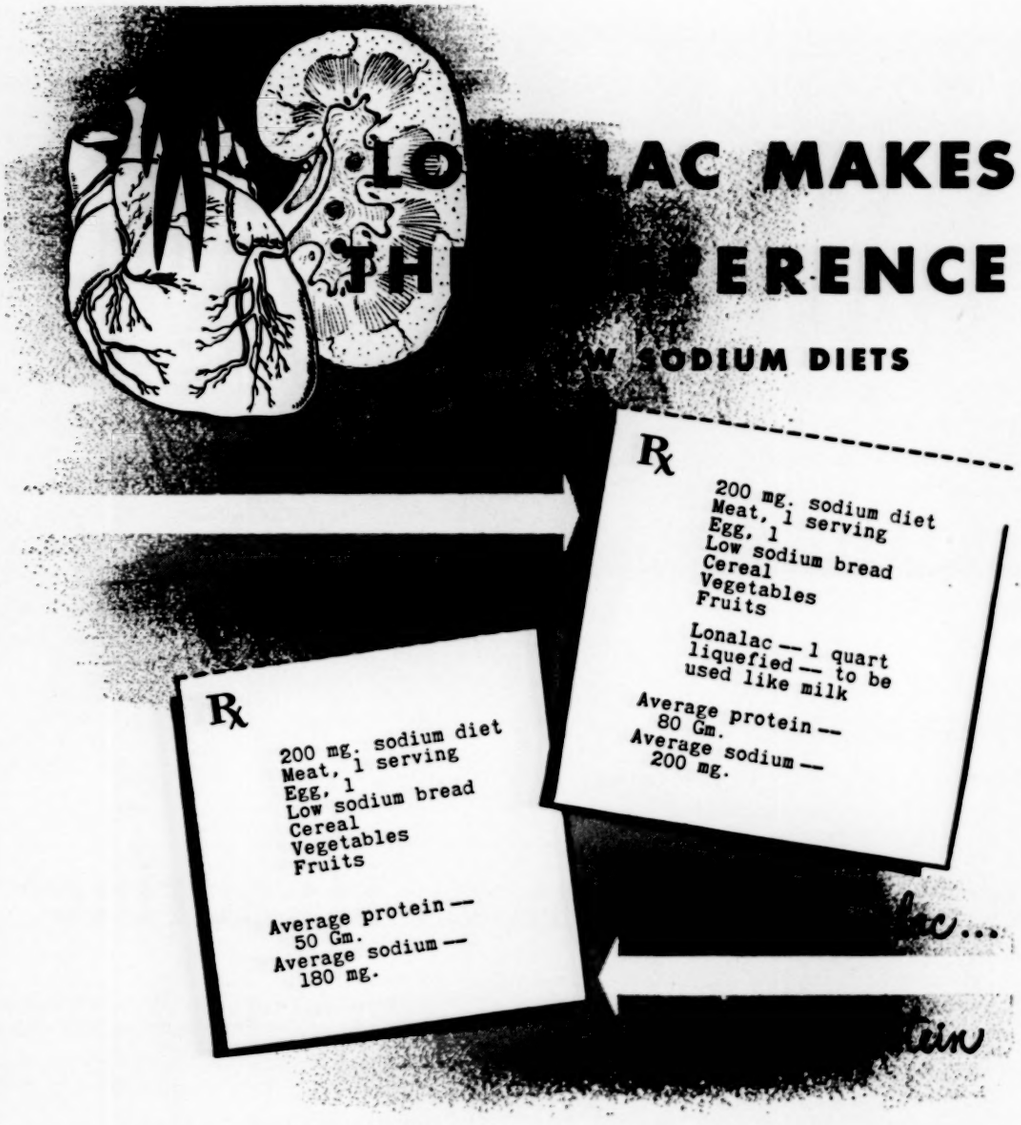

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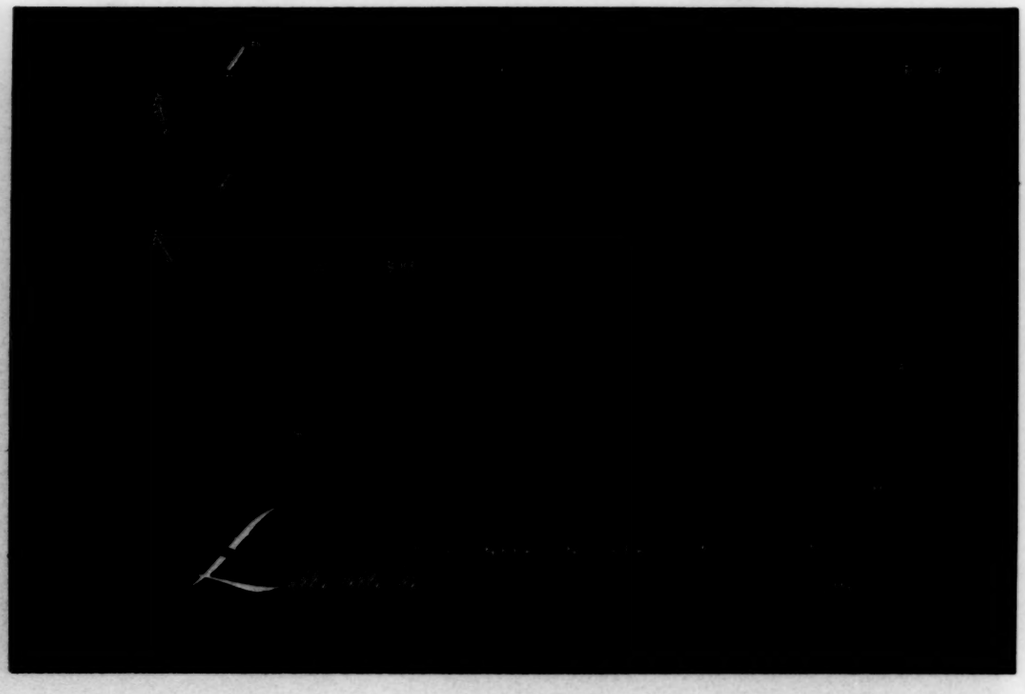

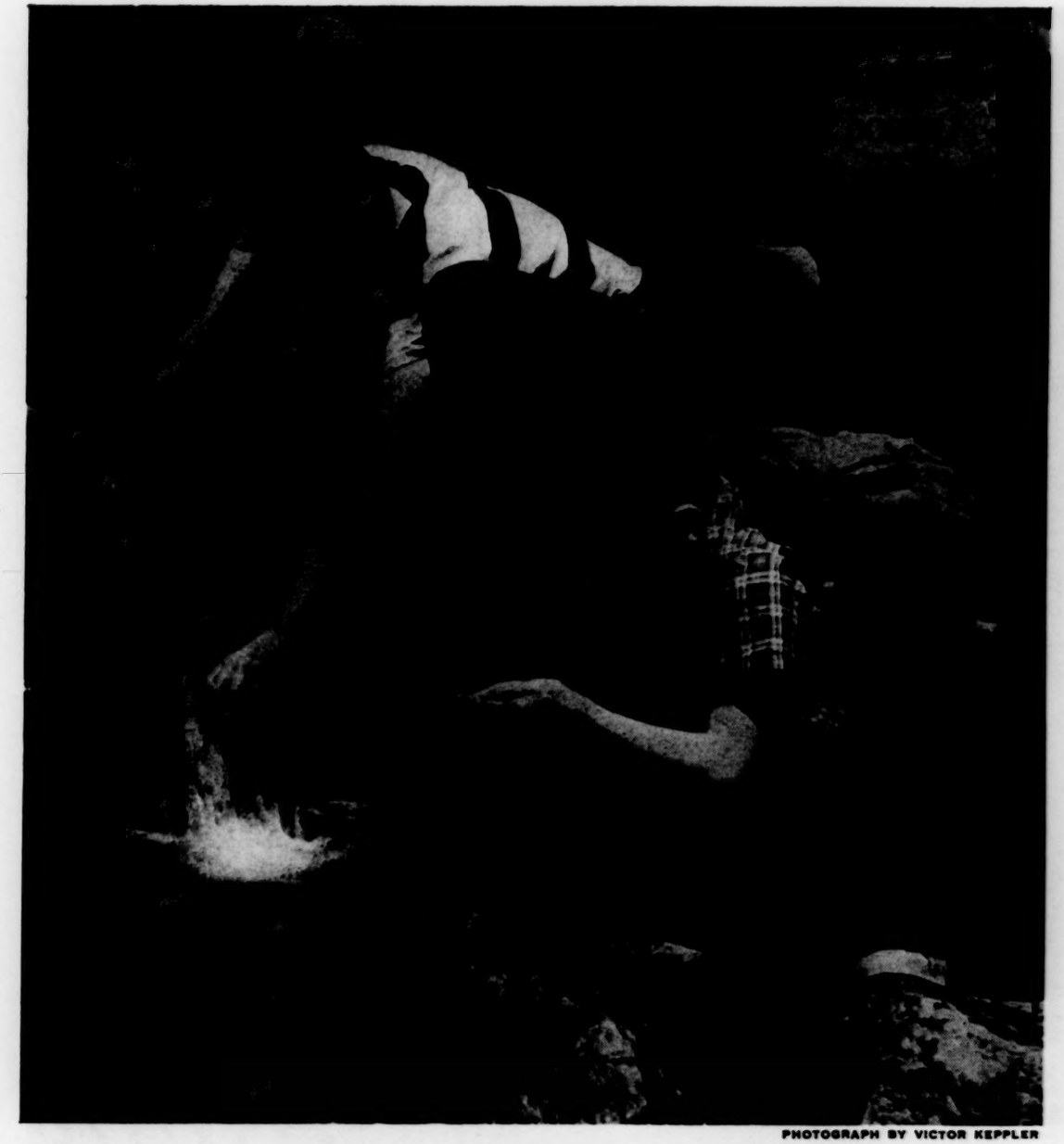

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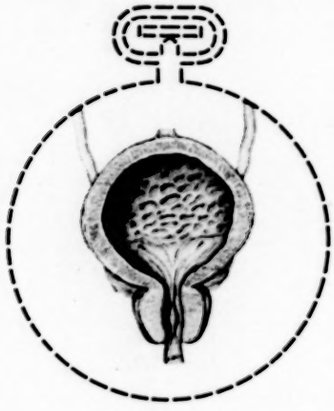

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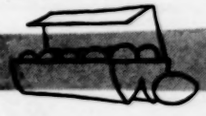

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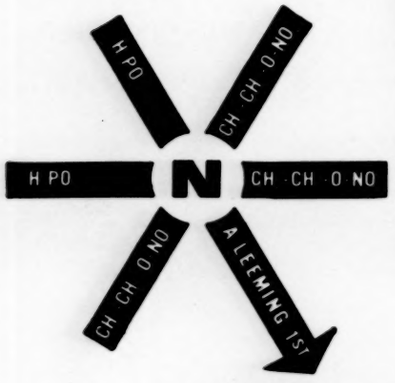

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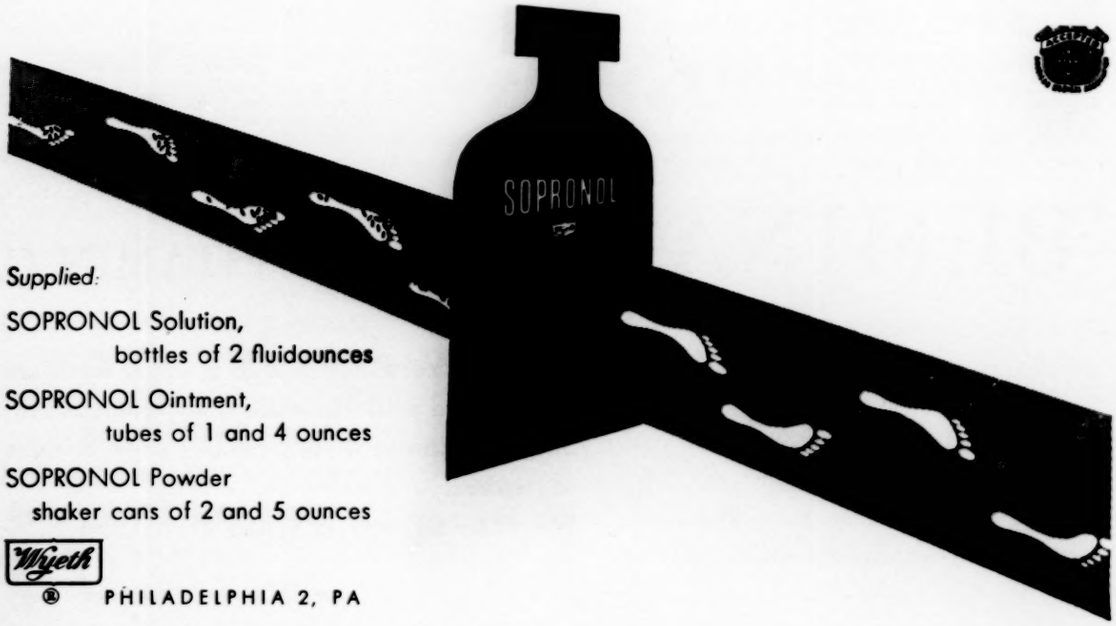

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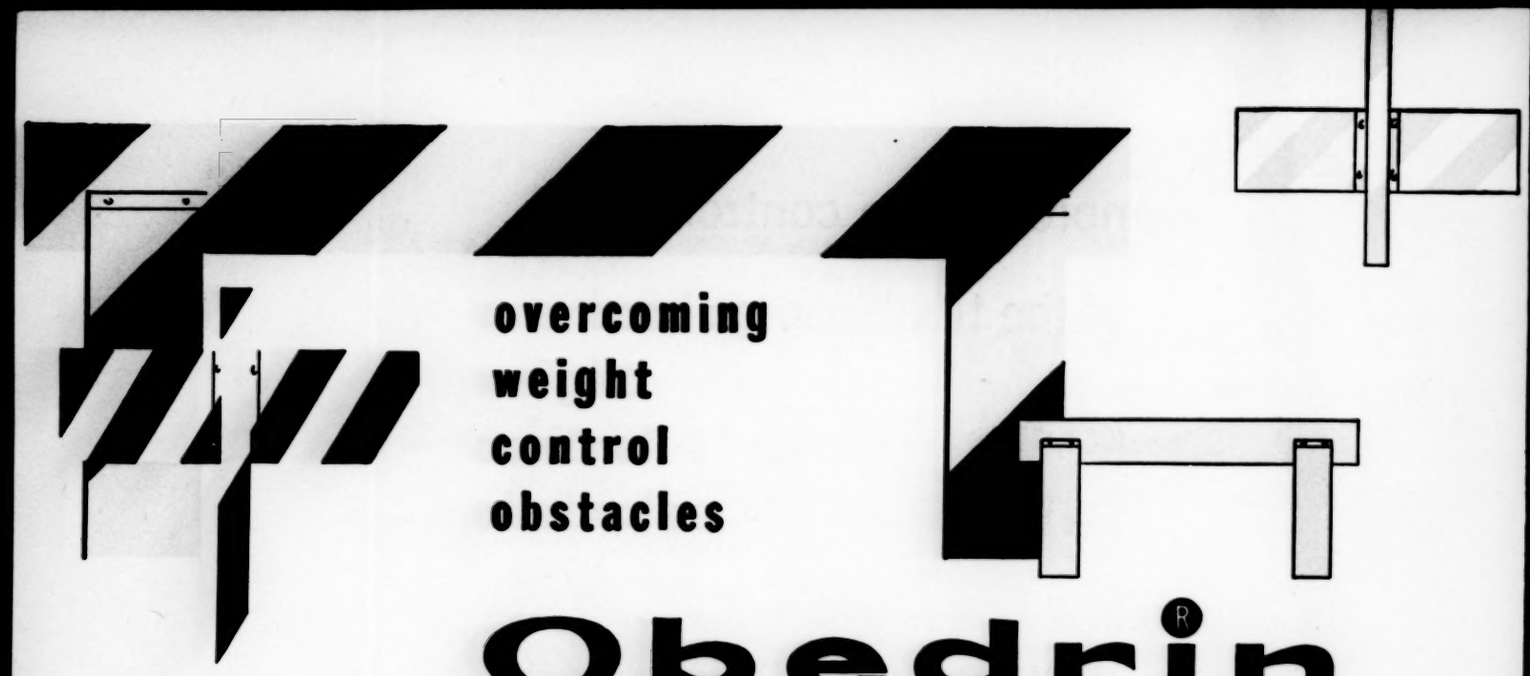

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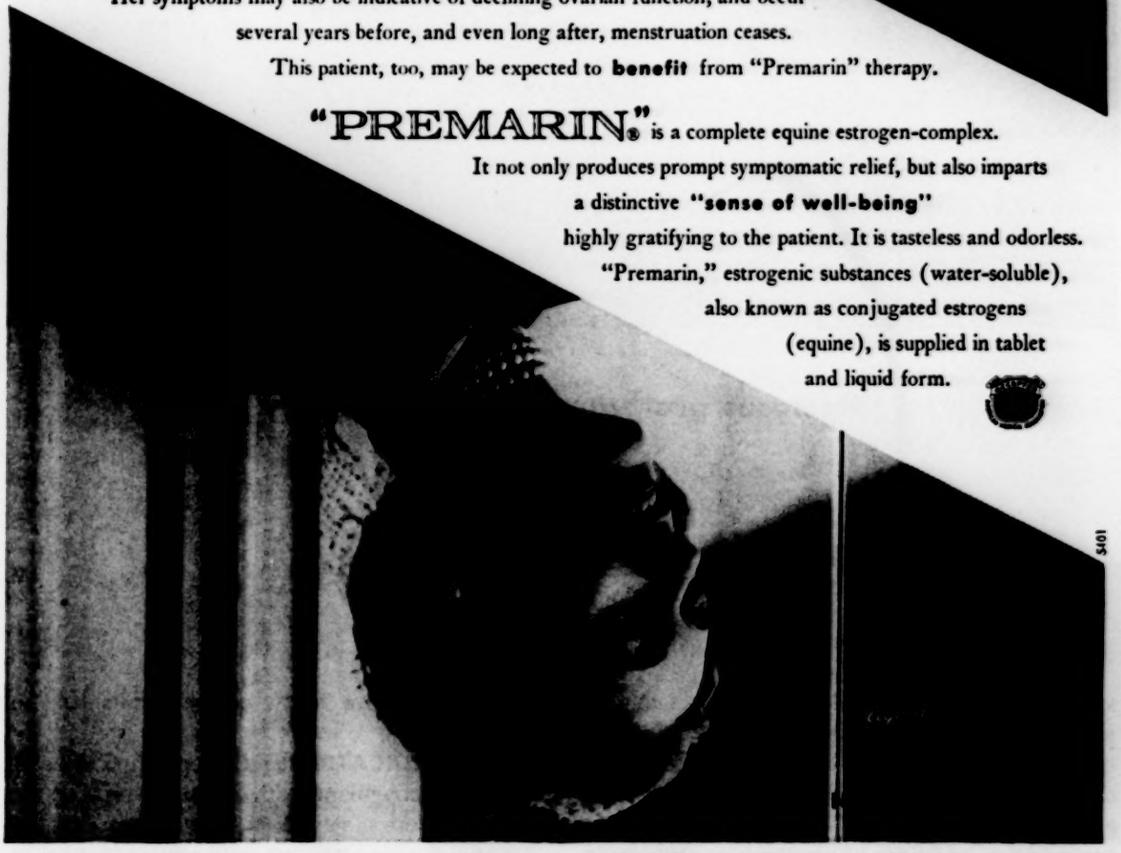

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*Kirsner, J. B.; Brandt, M. B., and Sheffner, A. L.: Diet and Amino Acid Utilization in Gastrointestinal Disorders, J. Am. Dietet. A. *29*:1103 (Nov.) 1953.

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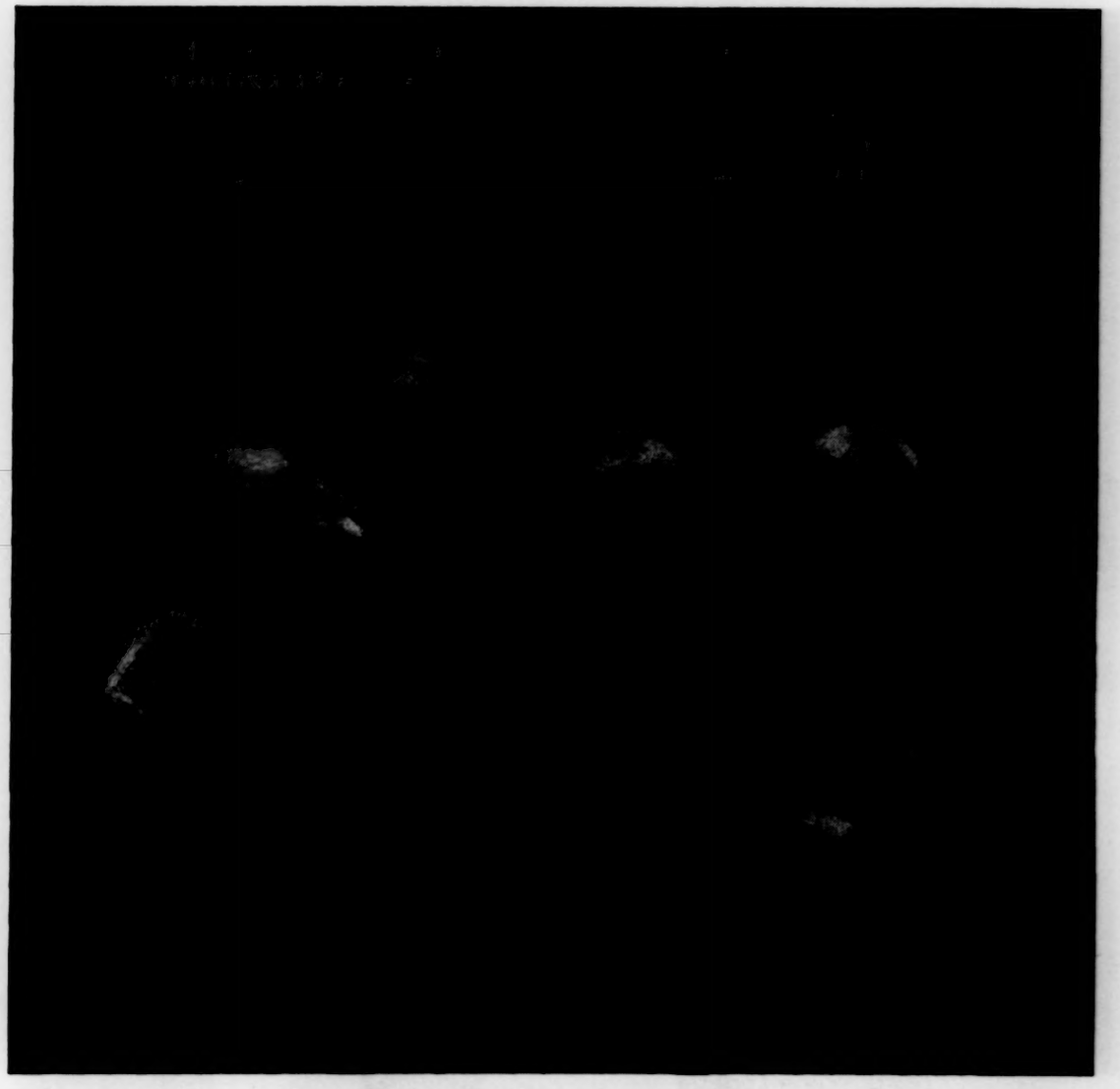

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virtually "nontoxic, well tolerated, and easy to administer."[1] Bacteria do not develop resistance to Mandelamine. It is economical for routine and sustained administration.

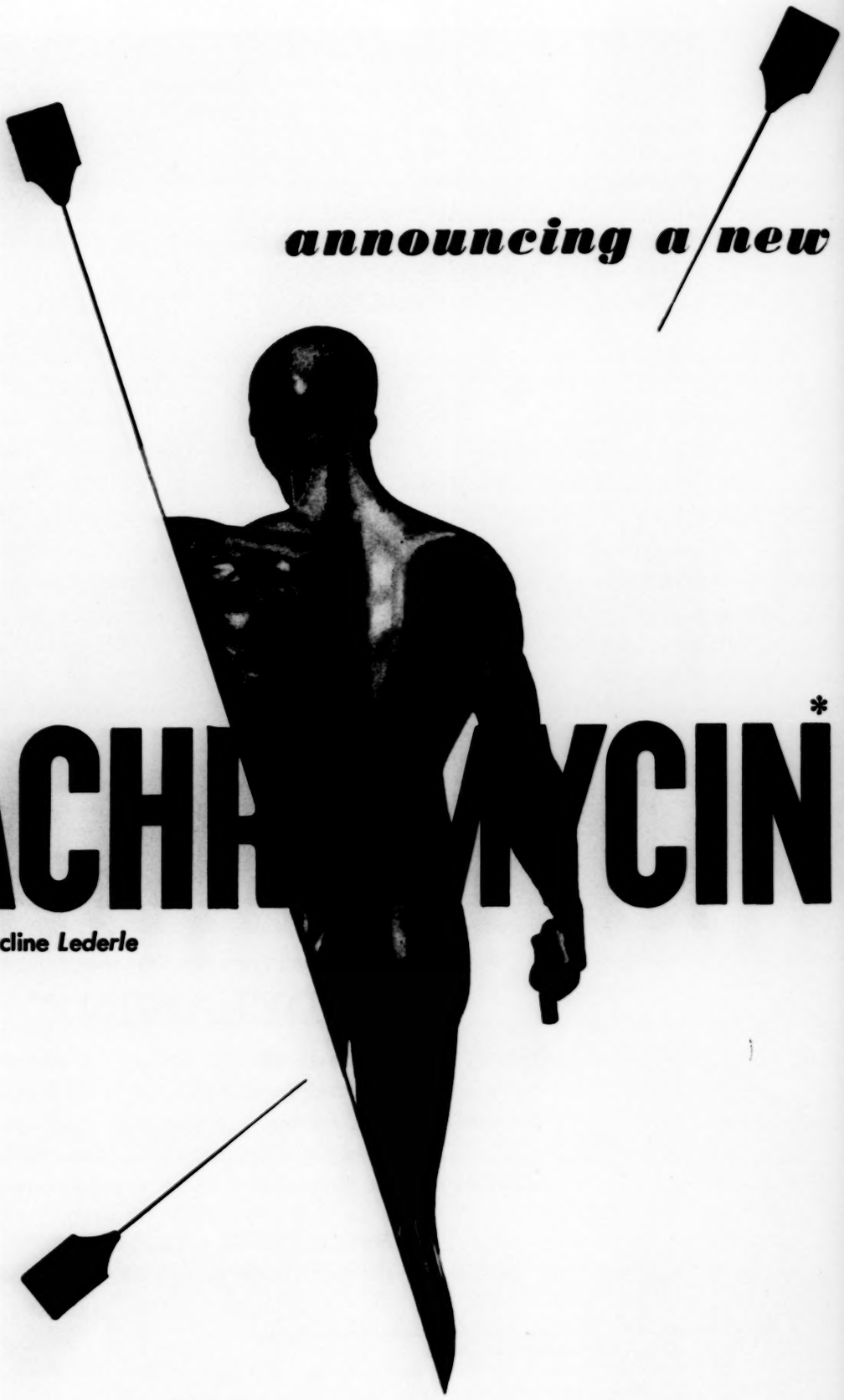
1. Carroll, G.; Allen, H. N., and Flynn, H.: Postgrad. Med. 8:312 (Oct.) 1950.

Adult dosage: 3 to 4 tablets t.i.d. *Children:* in proportion.

NEPERA CHEMICAL CO., INC.

PHARMACEUTICAL MANUFACTURERS, NEPERA PARK, YONKERS 2, N. Y.

"Mandelamine" is a registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.



announcing a new

ACHR MYCIN*

Tetracycline *Lederle*

therapeutic advance

At last, the many advantages of intramuscular administration of a broad-spectrum antibiotic have been fully realized. ACHROMYCIN, since its recent introduction, has been notably effective in oral and intravenous dosage forms. Now, after clinical testing, it is definitely proved highly acceptable for intramuscular use.

INTRAMUSCULAR

IMMEDIATE absorption and diffusion
PROMPT CONTROL of infection
CONVENIENT for the physician
NO UNDUE DISCOMFORT for the patient.

This new intramuscular form widely increases the usefulness of ACHROMYCIN, the broad-spectrum antibiotic of choice.

ACHROMYCIN Intramuscular is available in vials of 100 mg.

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Now...
new strength
Mesopin-PB
Tablets 5 mg.
homatropine
methylbromide
with 15 mg. pheno-
barbital. Also
now available
Mesopin (plain)
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for the "squeeze" of g.i. spasm

antispasmodic action
virtually without atropinism

through the selective spasmolysis
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Each yellow tablet of MESOPIN PB
or teaspoonful of yellow elixir
contains 2.5 mg. homatropine methyl-
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MESOPIN

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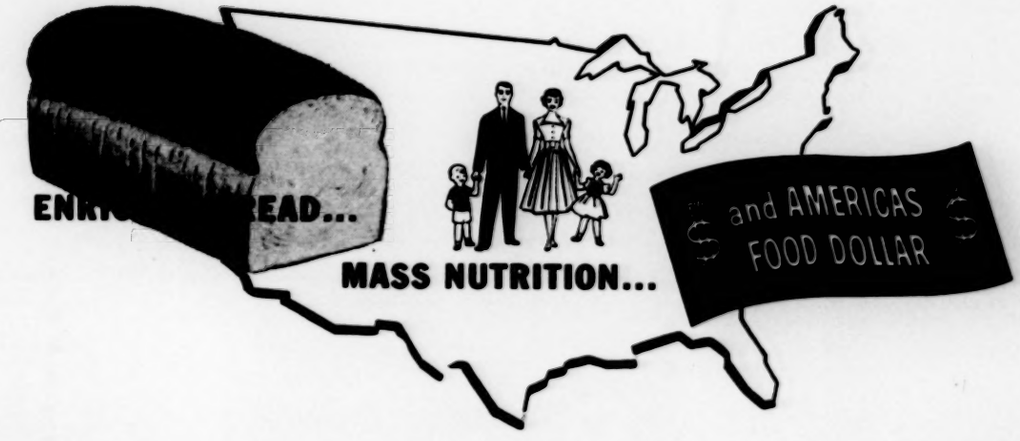

THE nationwide average retail price of 5½ ounces of enriched bread (the estimated average daily consumption) is approximately 5.8 cents.[1] This small fraction of America's food dollar has been responsible for notable gains in mass nutrition and health.[2] The National Research Council and the American Medical Association's Council on Foods and Nutrition have recently reaffirmed their endorsement of the enrichment of bread in the light of "good evidence that enriched bread has been beneficial to the public."[3]

Column I of the appended table shows the amounts of nutrients and nutrient energy provided by 5½ ounces of enriched bread. Column II gives the percentages of the recommended daily dietary allowance[4] available from this amount of enriched bread.

	Nutrients and Calories	Percentages of Allowances (1953)[4]
Protein	13.2 Gm.	20%
Thiamine	0.37 mg.	26%
Niacin	3.4 mg.	24%
Riboflavin	0.23 mg.	14%
Iron	4.1 mg.	34%
Calcium (average)	137 mg.	17%
Calories	418	14%

It is evident that enriched bread furnishes substantially more than its share of most nutrients. Thus it compensates for deficiencies of these nutrients in other foods of the everyday diet. Since virtually all enriched bread is made with nonfat milk solids, its protein—containing an average of 10.5 per cent milk protein and 89.5 per cent wheat and yeast proteins[5]—functions for growth as well as tissue maintenance.

Enriched bread might well be considered a basic food in maintaining the high nutritional status of the American people, yet it can be purchased for so small a percentage of the American food dollar.

1. Bureau of Labor Statistics, United States Department of Labor, Jan., 1954.
2. Sebrell, W.H.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.
3. Council on Foods and Nutrition, American Medical Association: A Statement of General Policy Concerning the Addition of Specific Nutrients to Foods, J.A.M.A. *154*:145 (Jan. 9) 1954.
4. Shank, R.E.: Revisions of the Recommended Dietary Allowances, J. Am. Dietet. A. *30*:105 (Feb.) 1954.
5. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, The Macmillan Co., 1952, pp. 212, 599.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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Cortril

brand of hydrocortisone

topical ointment

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brand of oxytetracycline

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because local anti-infective action is so often essential in combating superimposed secondary infection . . .

because anti-inflammatory action is so often essential for rapid symptomatic relief during anti-infective therapy . . .

This exclusive product contains the most consistently effective, anti-inflammatory hormone, CORTRIL—with the widely accepted, broad-spectrum antibiotic, TERRAMYCIN—in an elegant, easily applied ointment base.

supplied: ½-oz. tubes; 10 mg. CORTRIL (hydrocortisone) and 30 mg. TERRAMYCIN (oxytetracycline hydrochloride) per Gm.

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invitation to asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Tedral provides:

Theophylline	2 gr.
Ephedrine HCl	3/8 gr.
Phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

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